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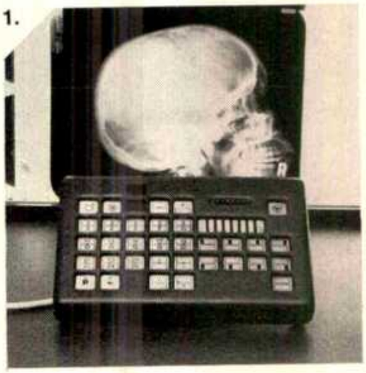

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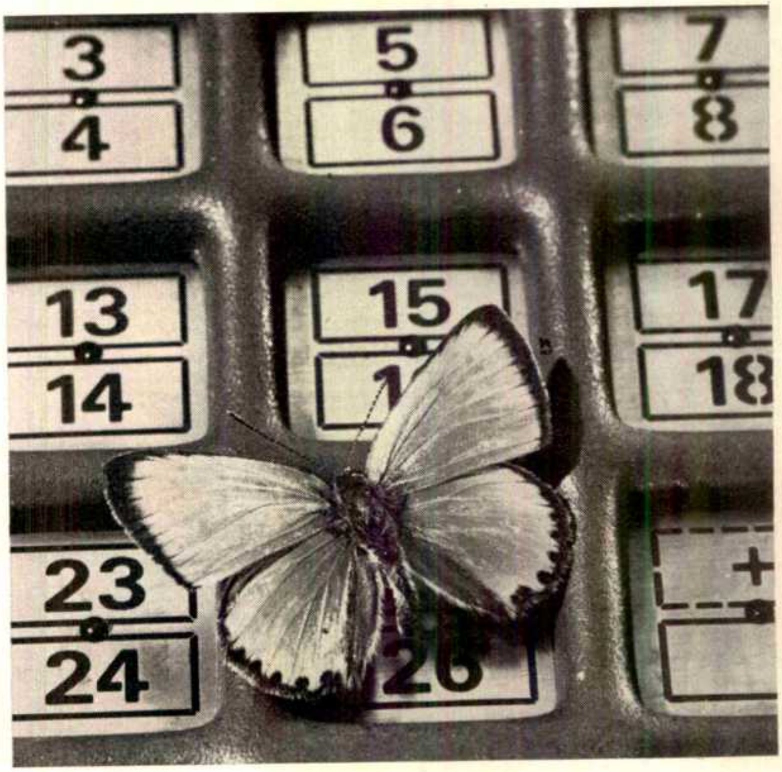

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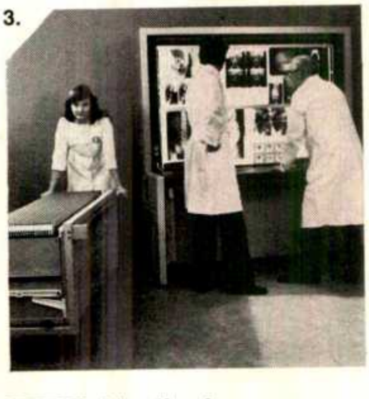

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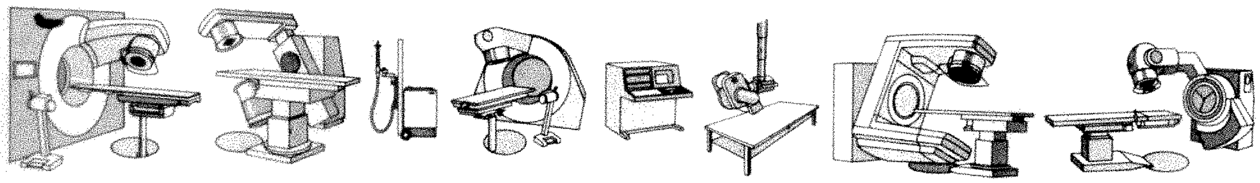

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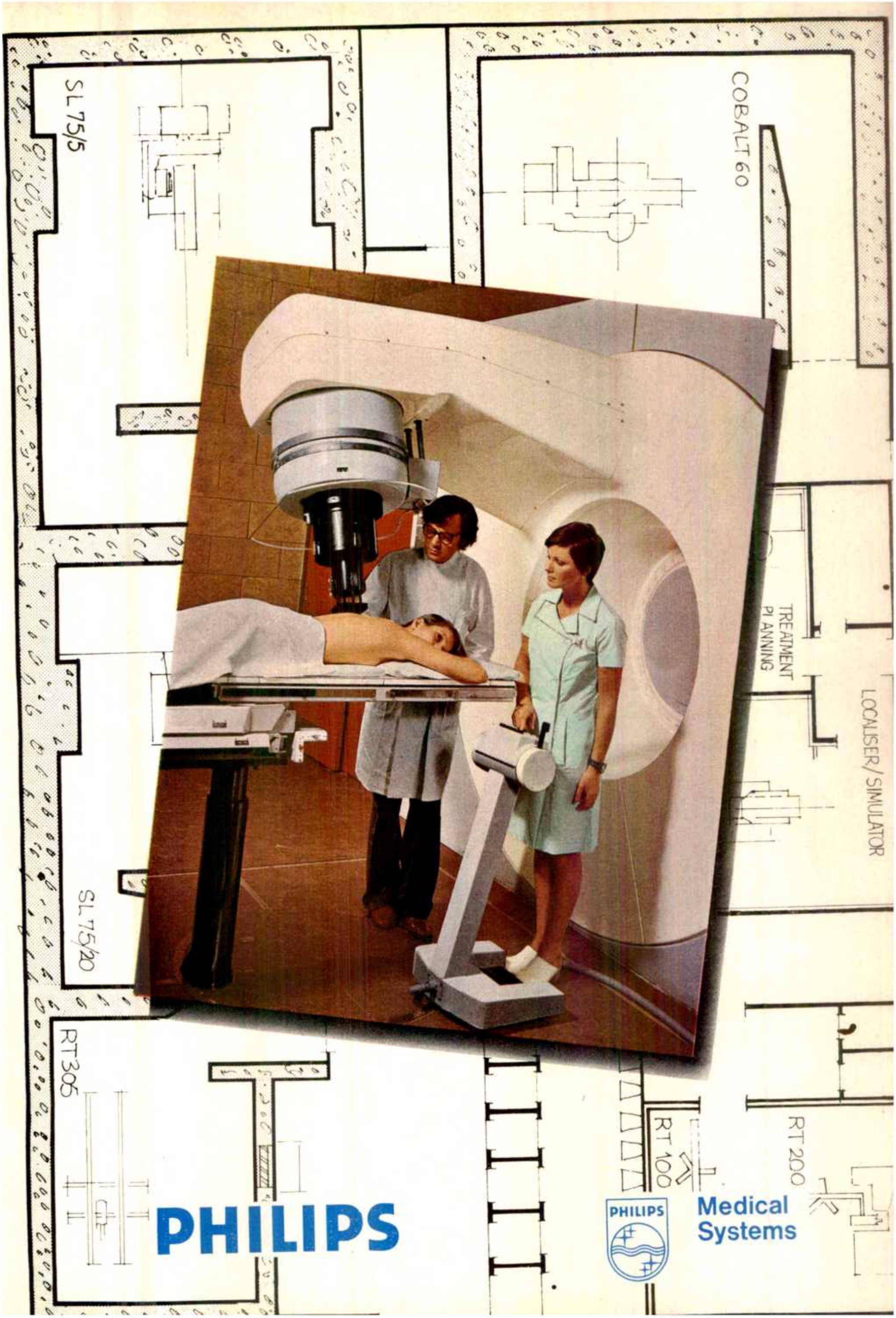

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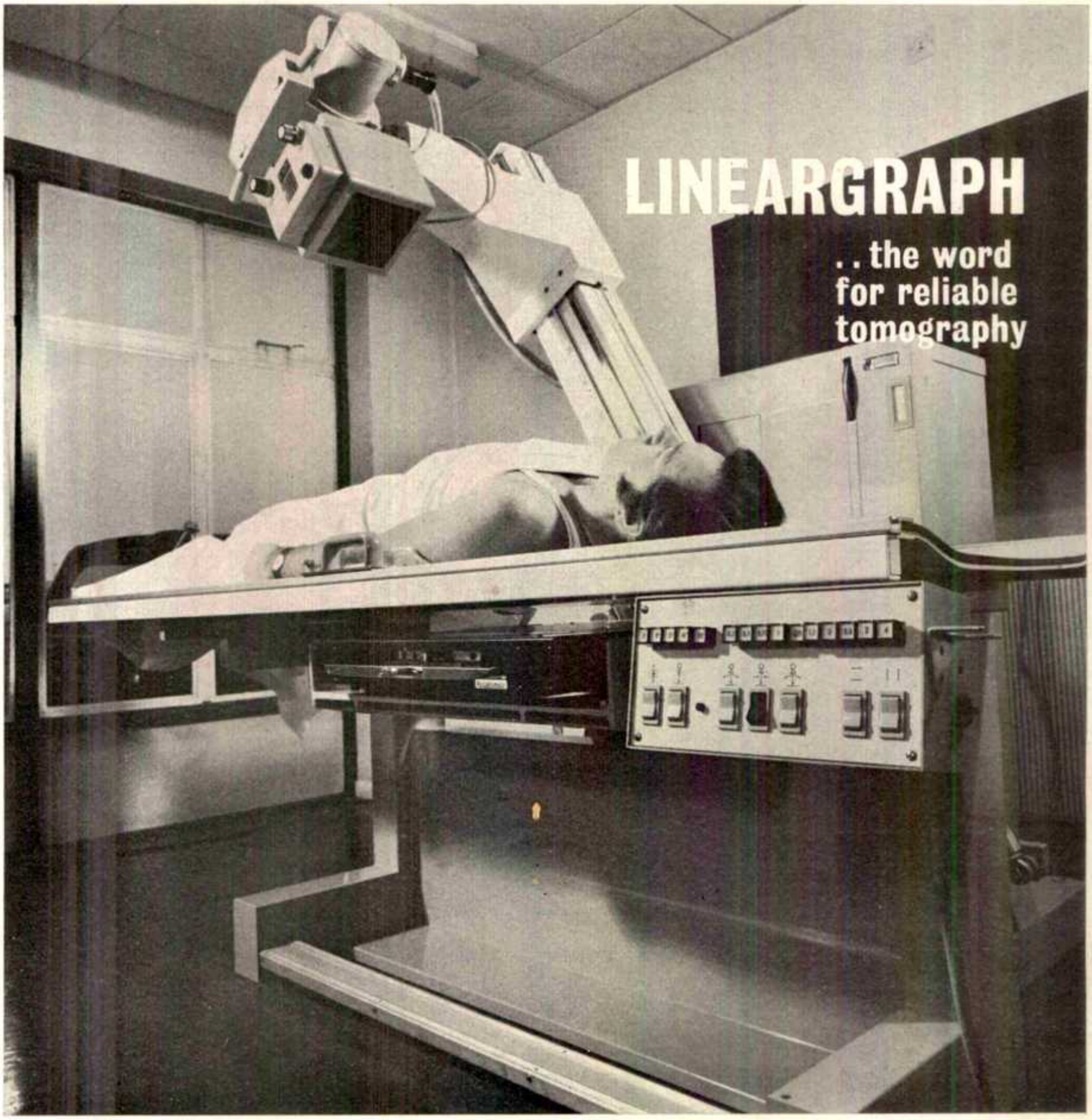

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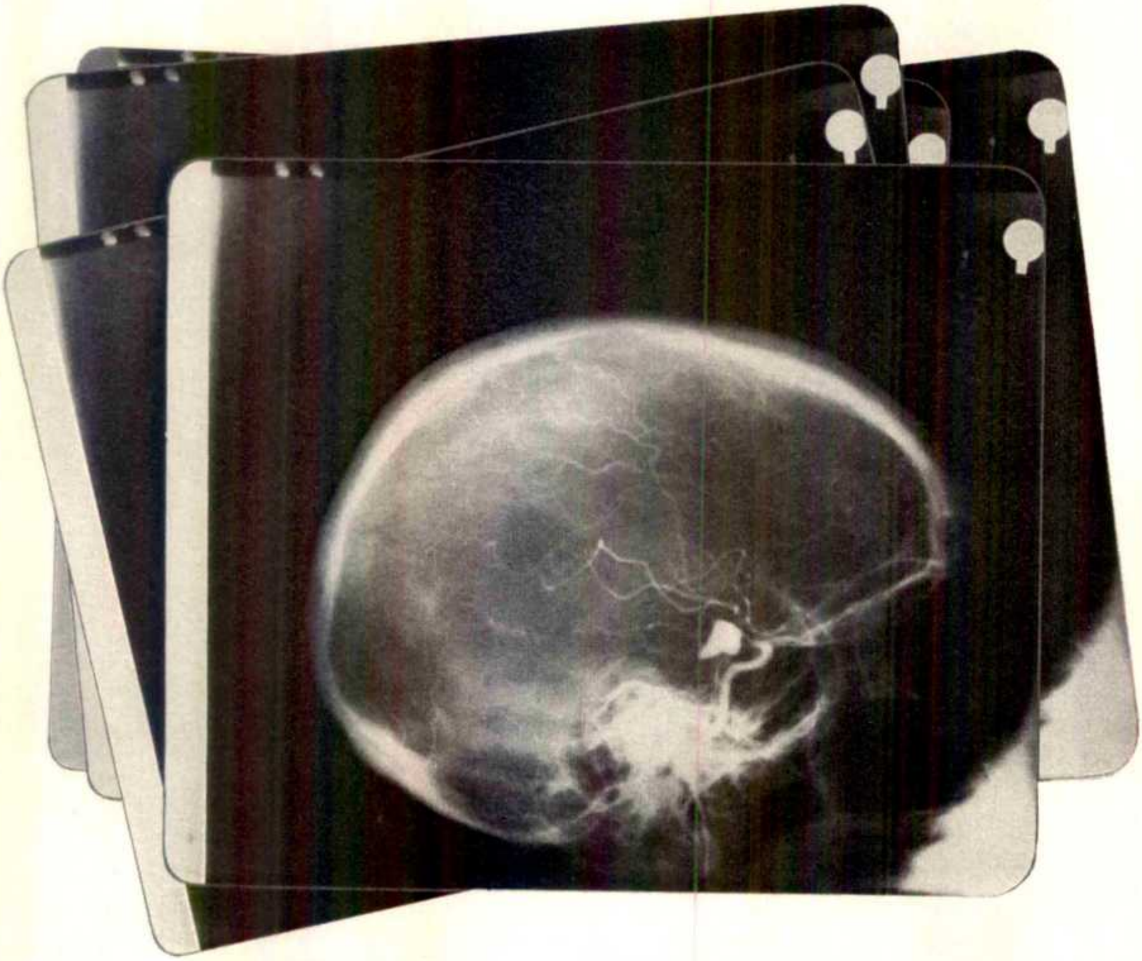

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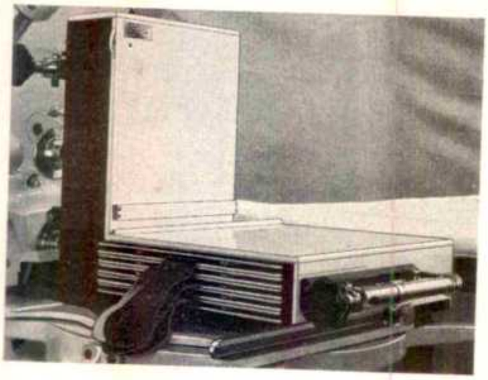

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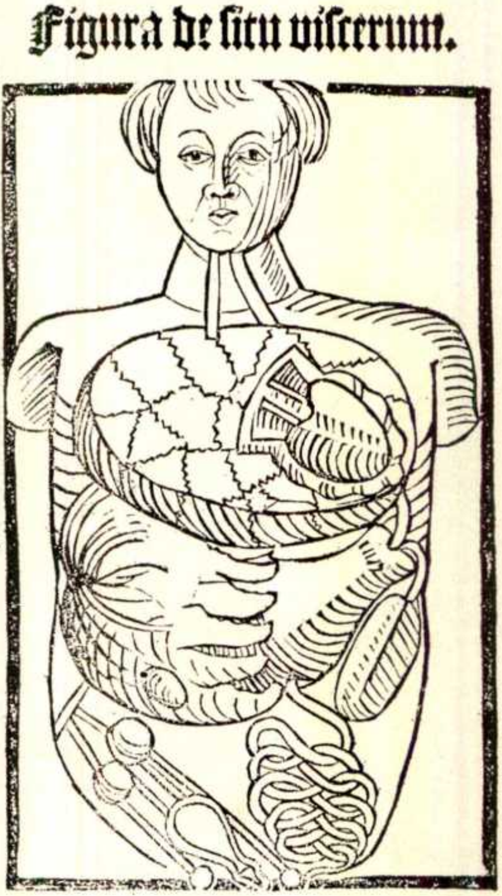
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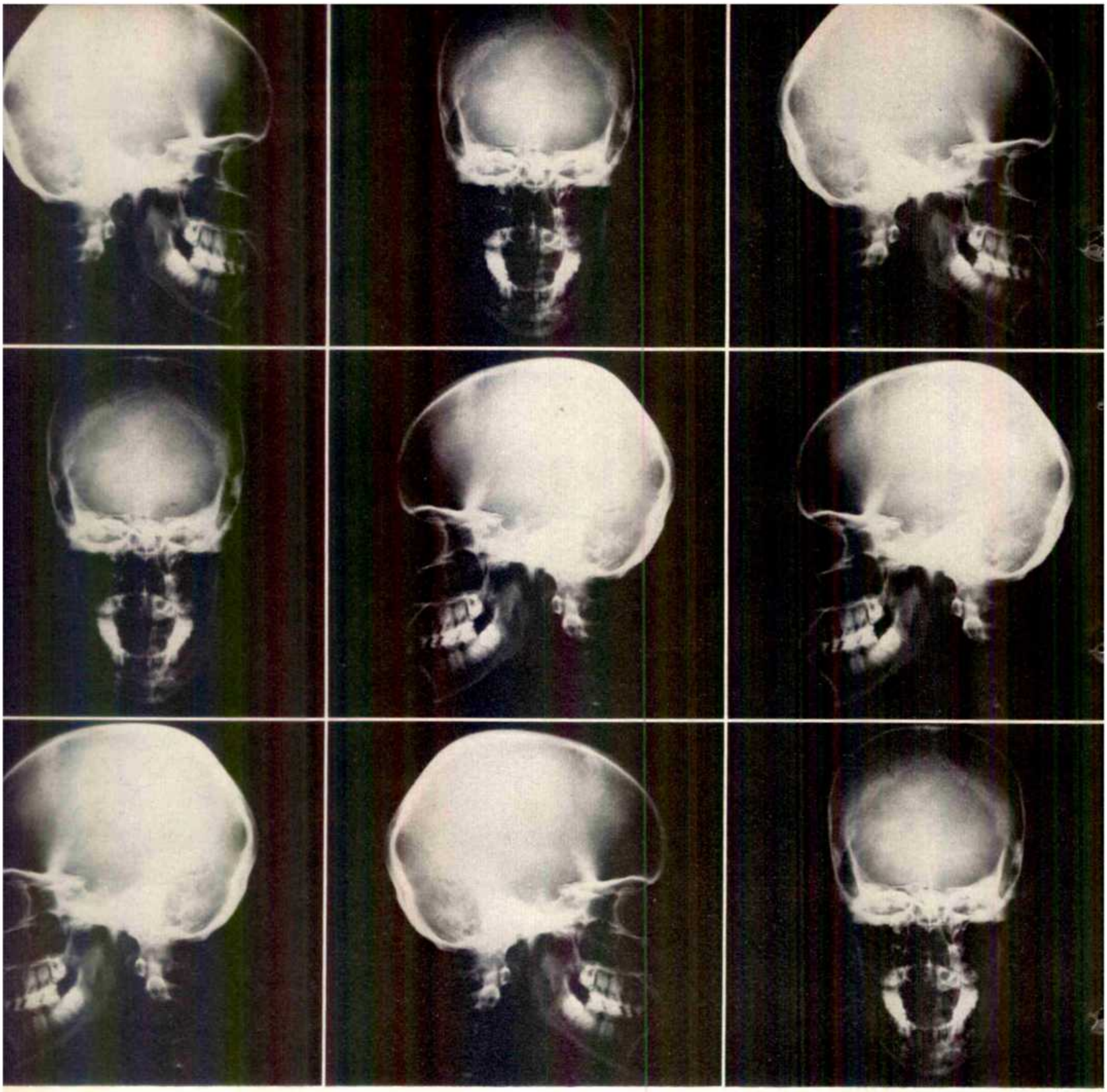

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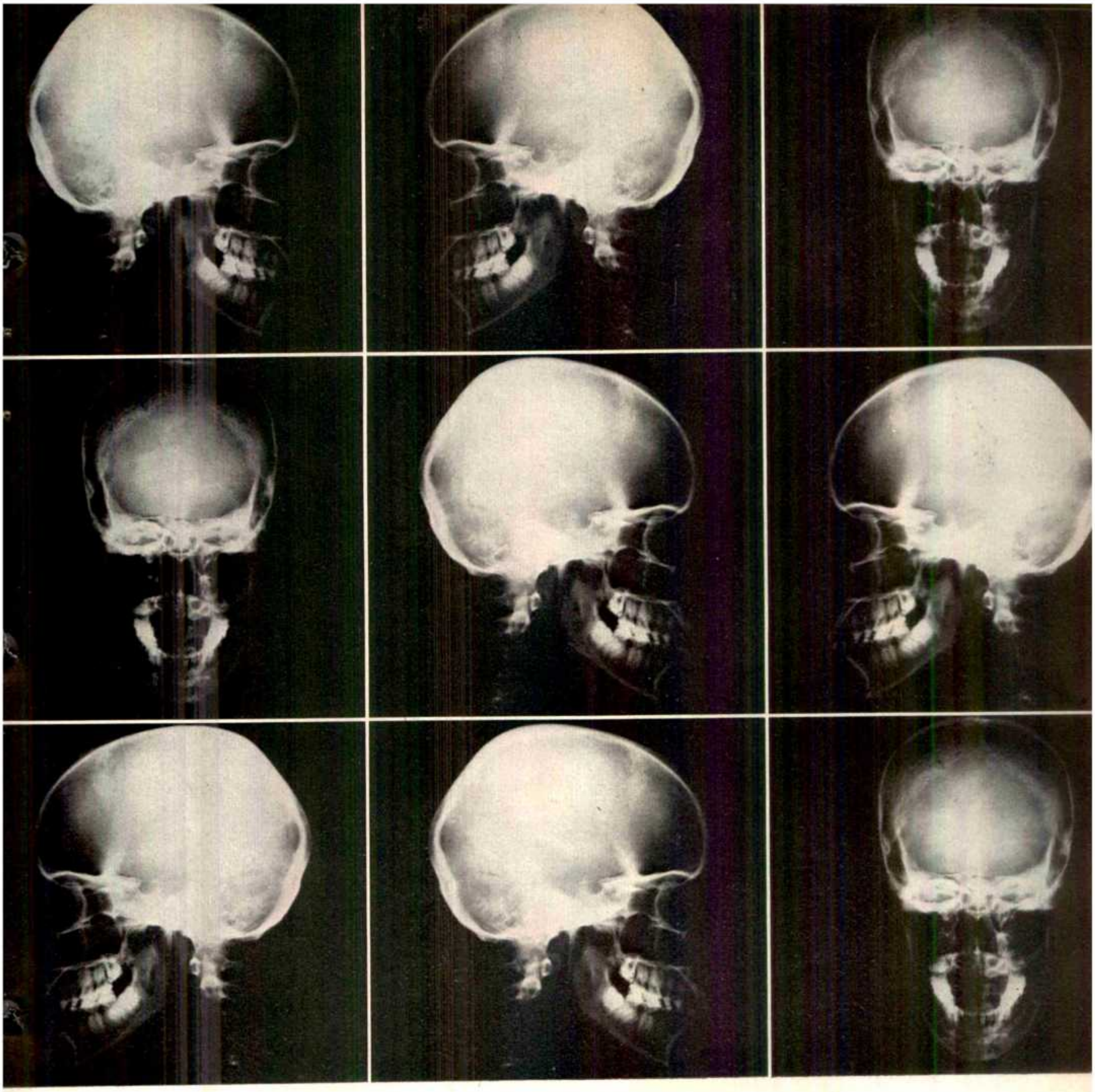

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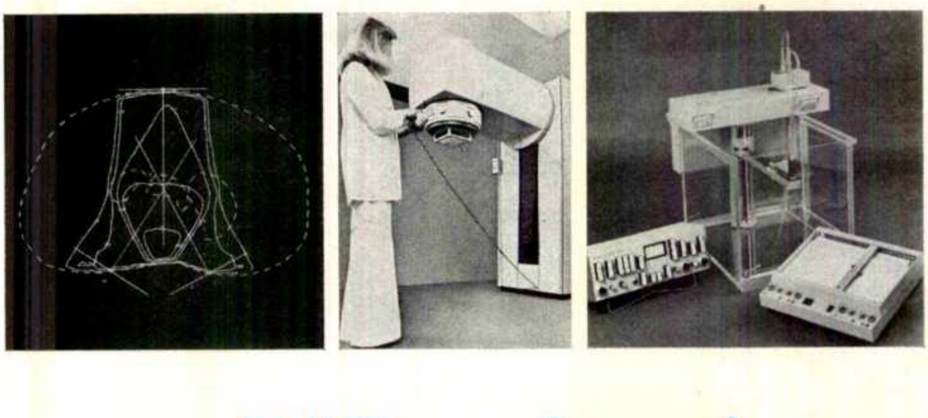

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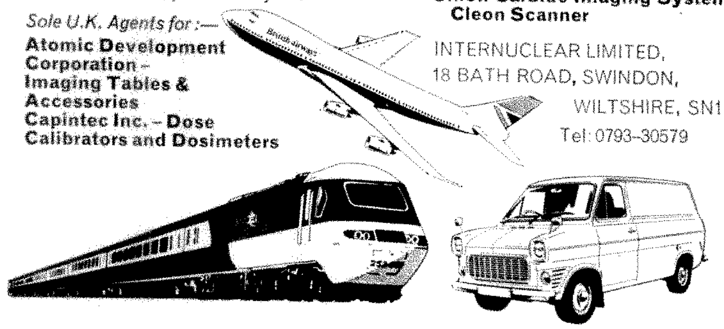

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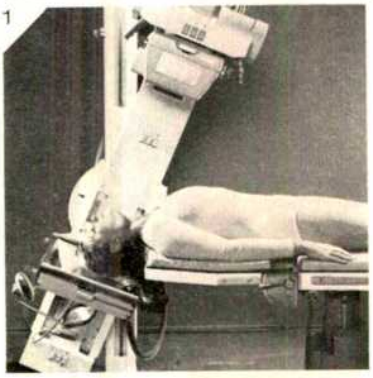

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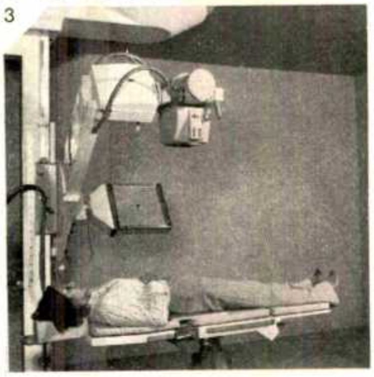

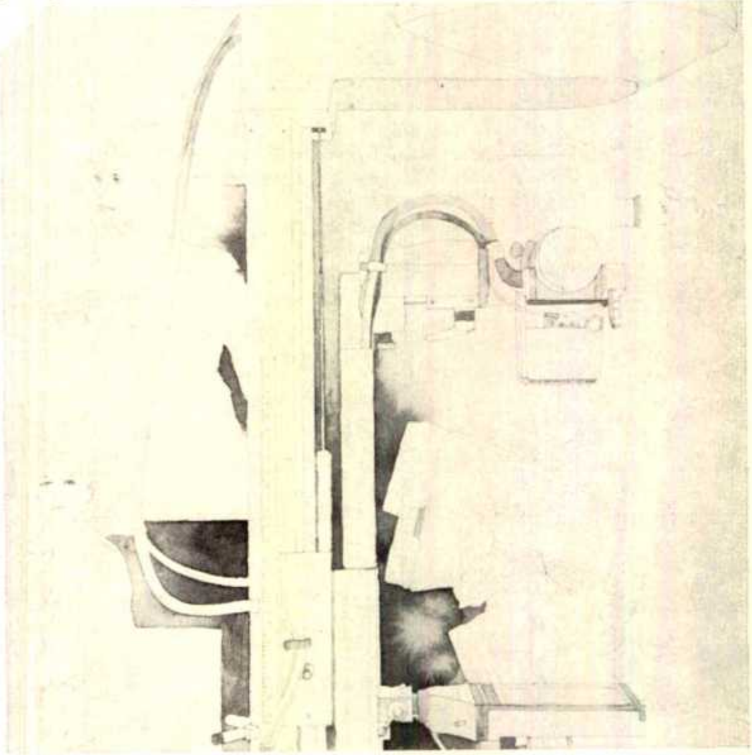

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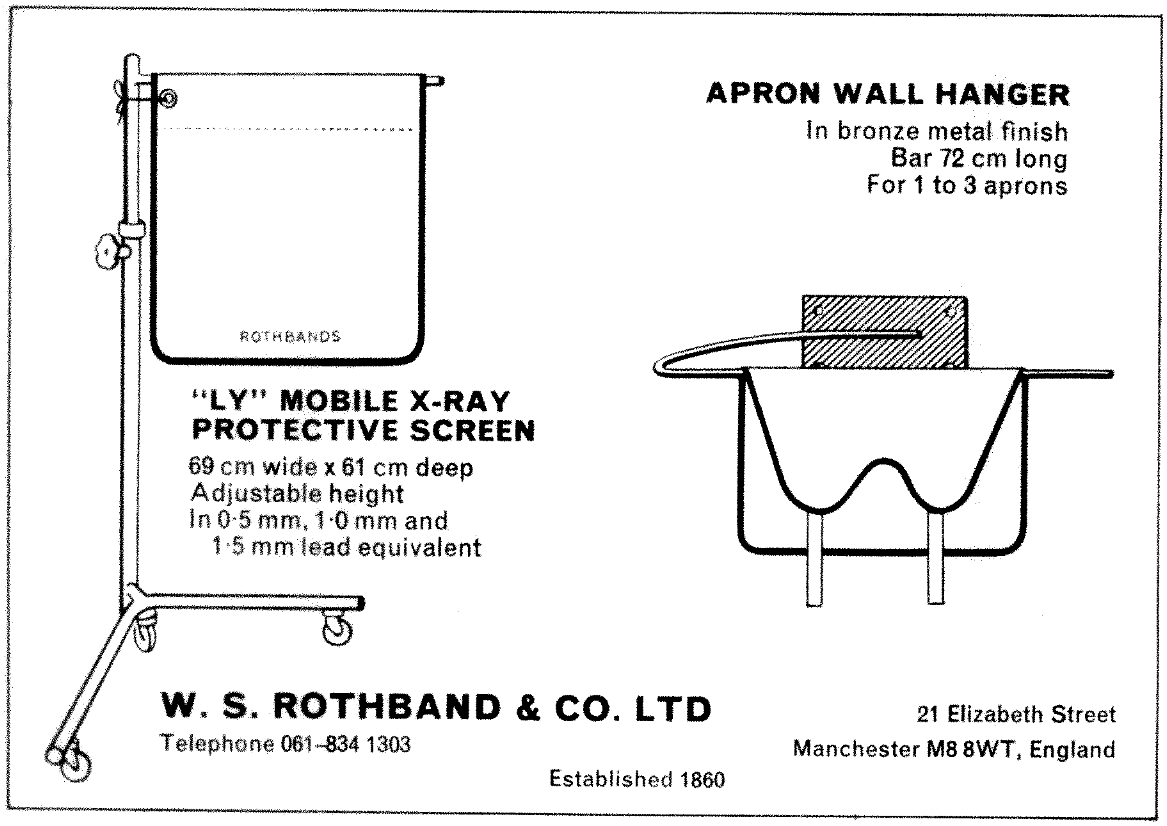

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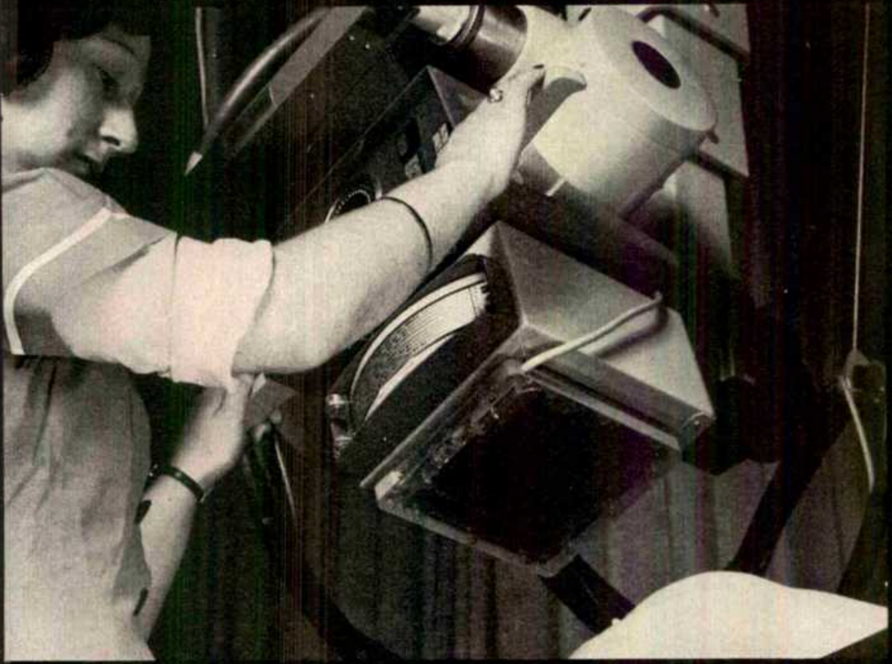

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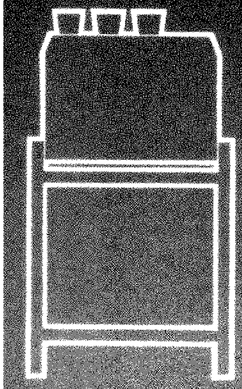

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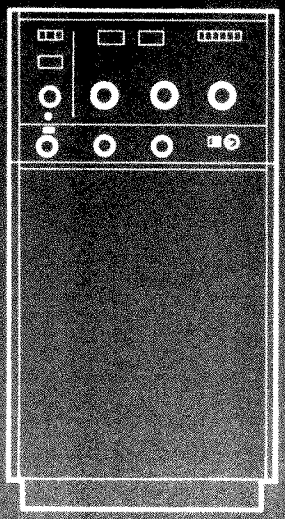

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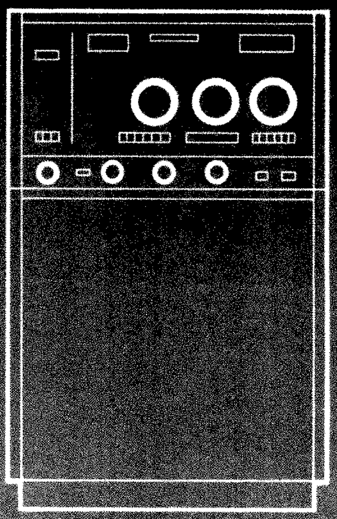

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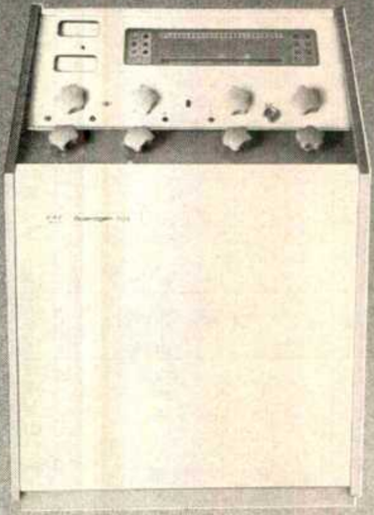

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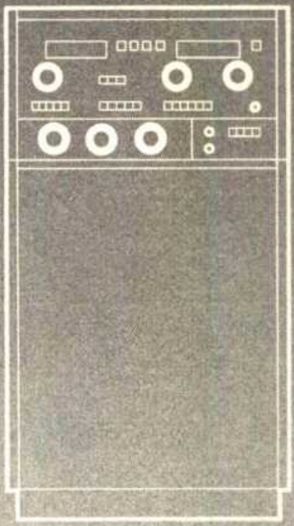

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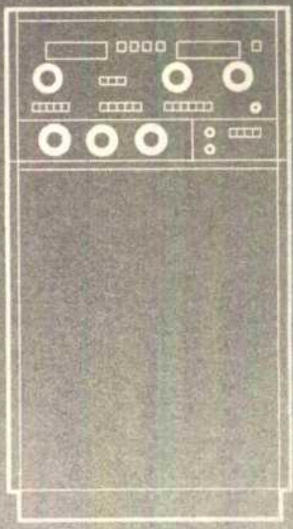

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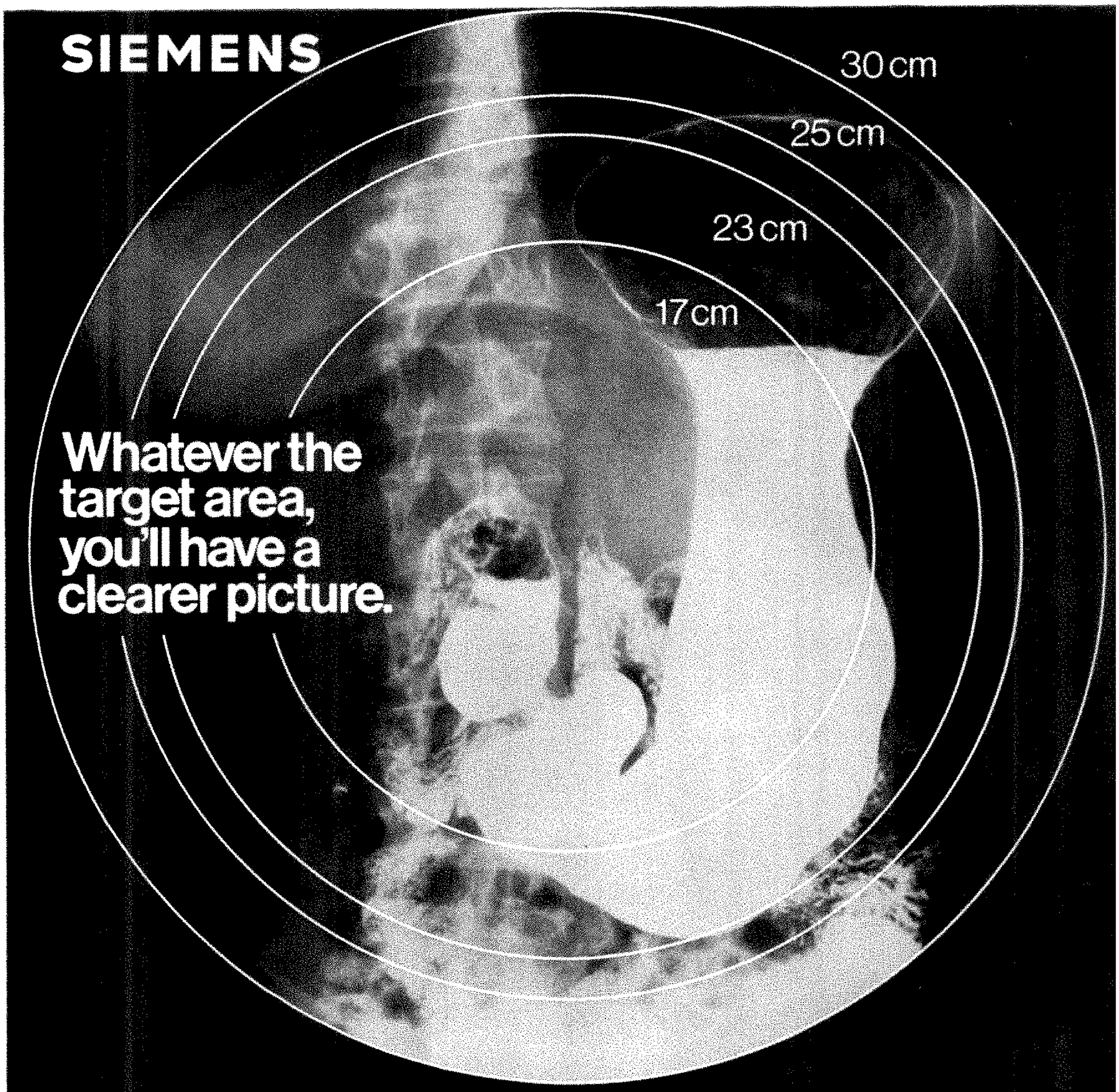

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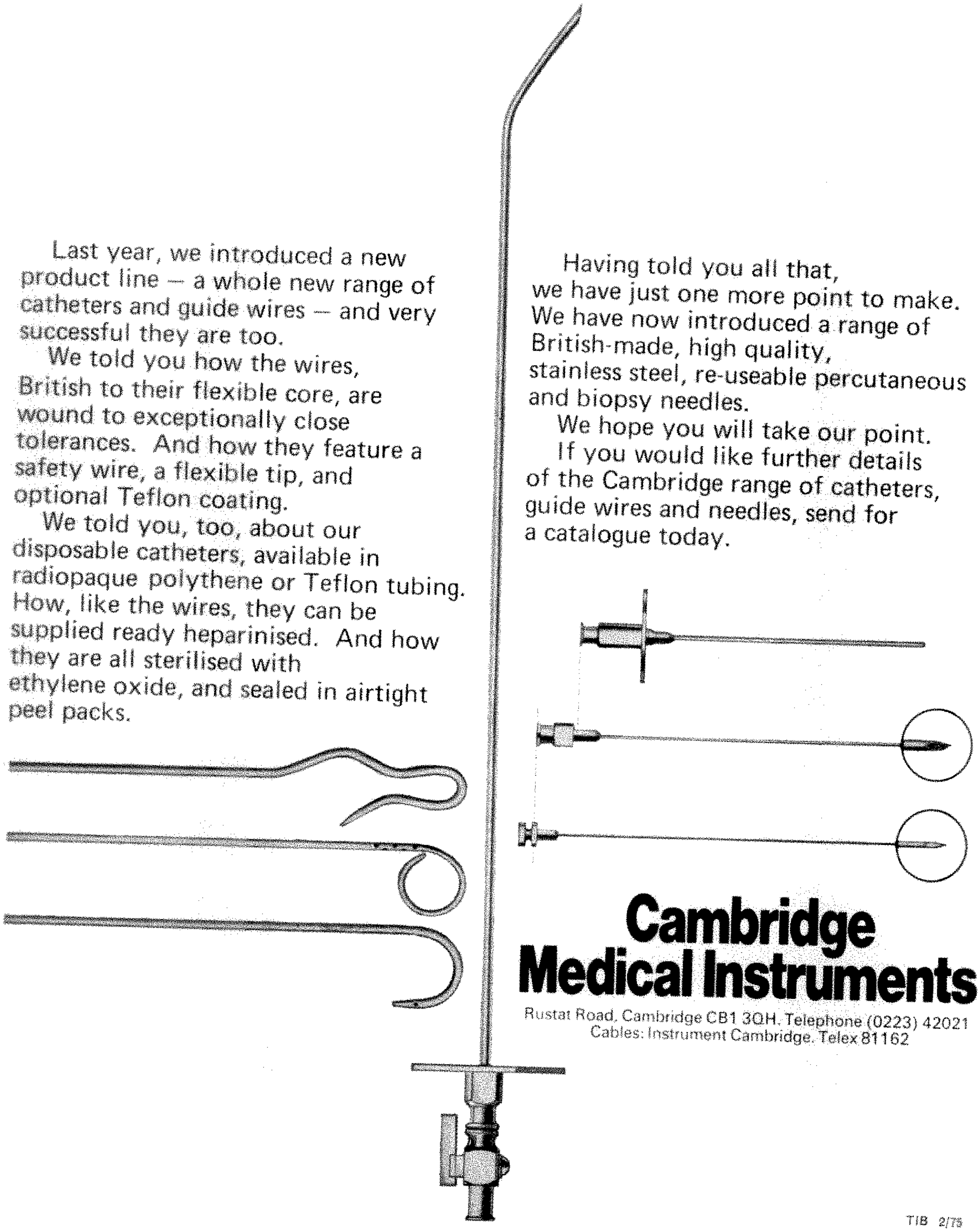

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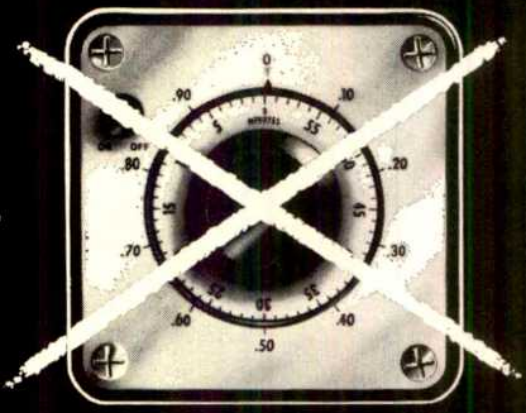

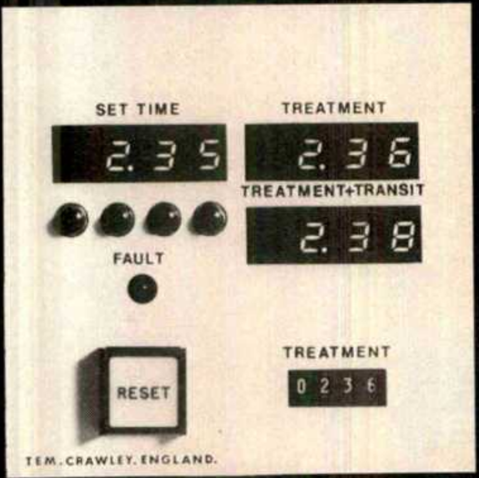

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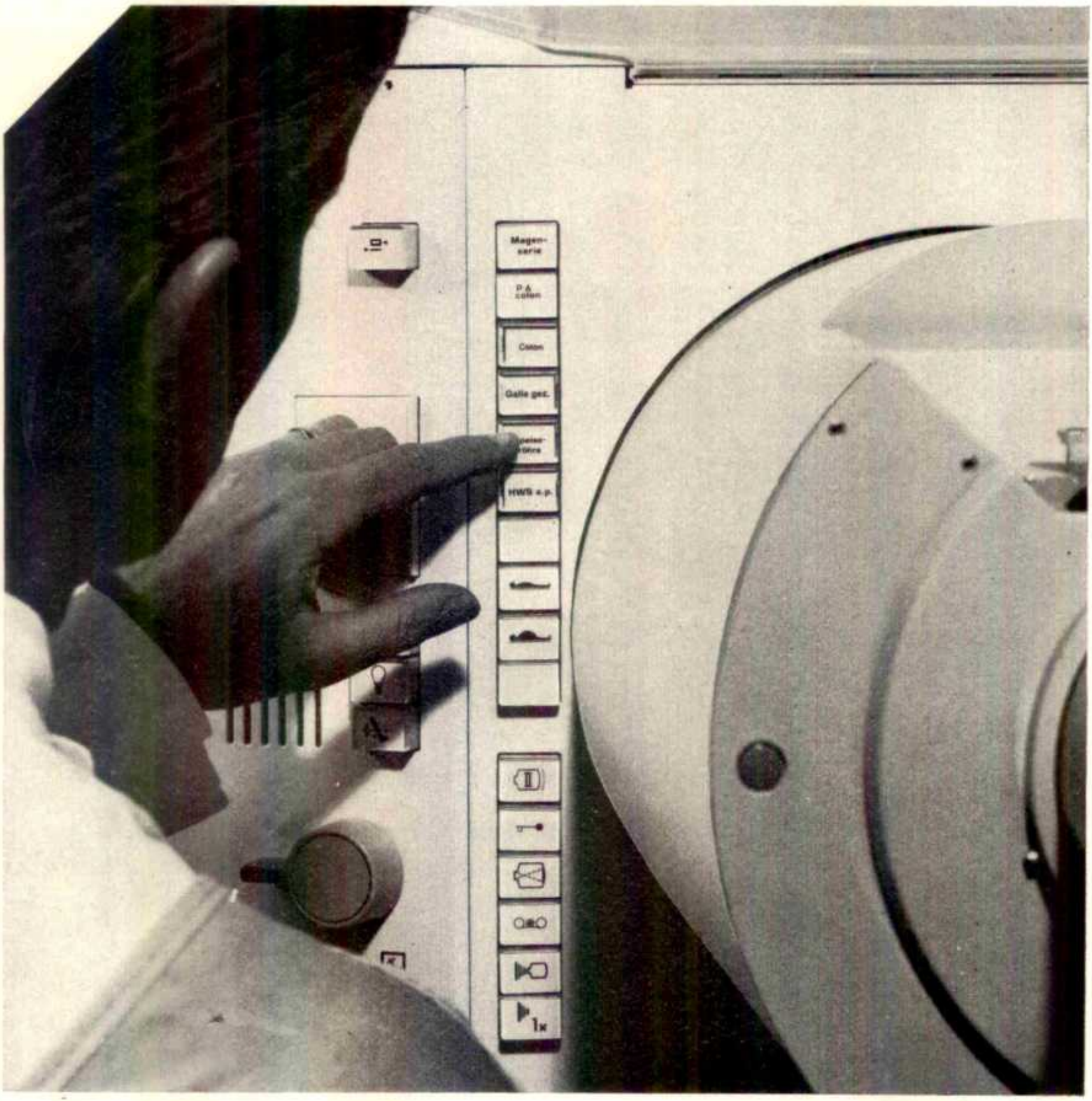

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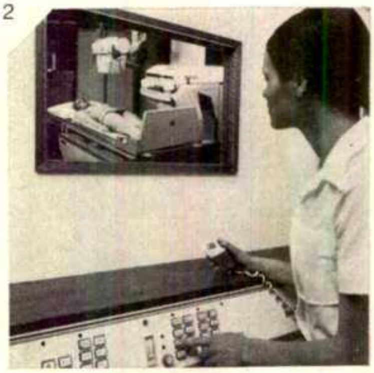

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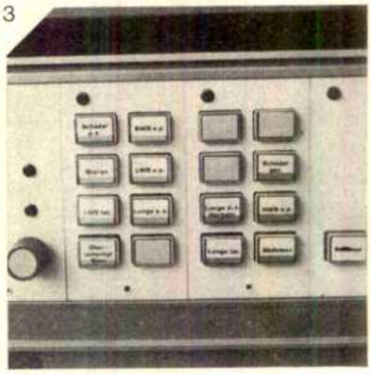

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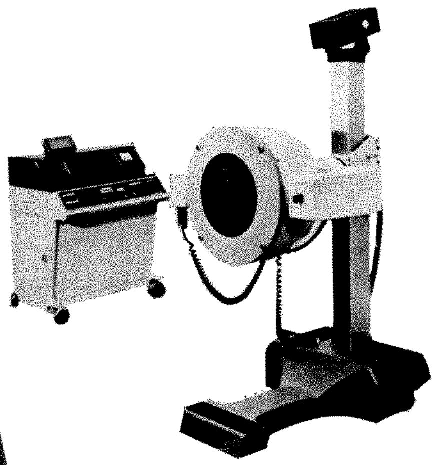

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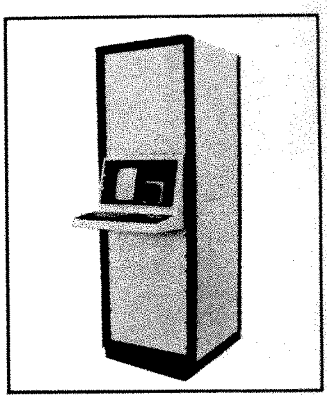

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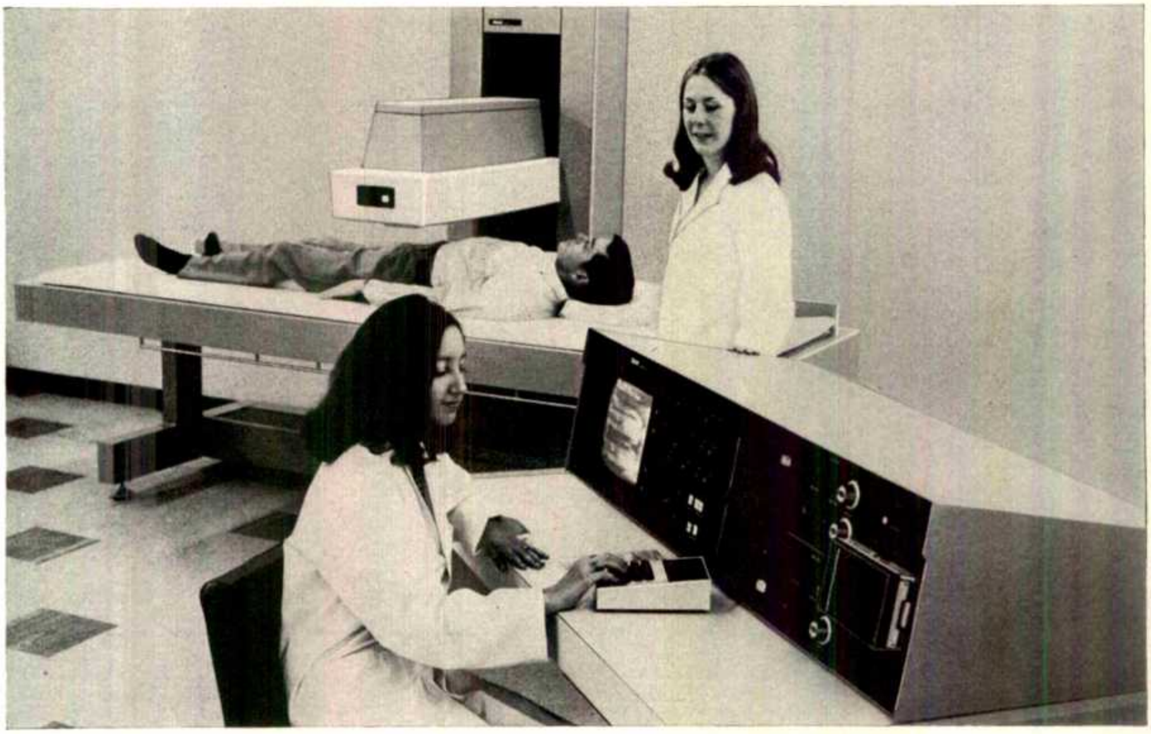

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VOLUME 50 NUMBER 590 FEBRUARY 1977

The British Journal of Radiology

Radiology now

Osteoarthrosis of the hip: one disease or many?*

Osteoarthrosis of the hip is a common disorder. In Kellgren's (1961) population study, approximately 20% of people over the age of 55 years showed evidence of osteoarthrosis of the hip. The morbidity in the middle-aged white subject is considerable (Sze, 1963), but surveys of prevalence and morbidity are bedevilled by the lack of internationally recognized clinical criteria, and imprecision in radiological interpretation.

Though the disease is so common, aetiology and pathogenesis are ill understood. This is reflected in nomenclature. Osteoarthritis is a well-established name, but there is no suggestion that the disorder is primarily inflammatory in nature, and osteoarthrosis is preferred by many. Degenerative disease of the hip is an unwieldy term and covers such a broad spectrum that its precise meaning is uncertain.

A disease is generally authenticated by the establishment of a specific natural history and characteristic pathological changes.

Traditionally, osteoarthrosis has been separated into primary and secondary types; the term secondary osteoarthrosis is applied where change is superimposed on a preceding abnormality of the hip. Secondary osteoarthrosis therefore follows local trauma, dysplasia, aseptic necrosis, inflammatory arthritis, etc. If it is assumed that the normal hip is ideally suited for load-bearing, then even slight alteration in the convex–concave surfaces may result in inequable distribution of compression forces over the articular surface (Bullough *et al.*, 1973; Goodfellow and O'Connor, 1975). Further studies are proceeding, but at present the relevance of altered local stress is not proven.

Of great interest is the suggestion that *minor* joint dysplasia or deformity may predispose to degenerative change. It is possible, radiologically, to recognize the shallow sloping dysplastic acetabulum, and although it is not proven that such patients form part of the spectrum of congenital dislocation *per se*, alterations in joint mechanics may result in osteoarthrosis.

Murray (1965), postulating that minor anatomical abnormalities may lead to so-called primary osteoarthrosis, has drawn particular attention to the "tilt deformity" in certain femoral heads affected by degenerative change. In this group of patients, the femoral head bears a resemblance to the slipped femoral capital epiphysis. Murray believes that in these hips an unrecognized minor epiphyseal slip has occurred in adolescence, leading to osteoarthrosis in middle age. Whilst the concept may be valid, this exclusive aetiology of the tilt deformity is in dispute. Meachim *et al.* (1972) have shown clearly by slab radiographs that such a deformity may be produced by downgrowth of an osteophyte from the inferior margin of the femoral head. This results logically from the common upward migration of the femoral head with osteophyte growth in an area of low joint stress (Harrison *et al.*, 1953). No evidence is forthcoming to indicate that an osteophyte itself causes displacement of the femoral head. A similar patho-radiological study has been performed by Resnick (1976). The author suggests that changes in the acetabulum may initiate the tilt deformity rather than epiphyseal slip in adolescence. Murray and Duncan (1971) did further work on the presence of tilt deformity in adolescents and related it to athletic activity. This careful study suggested that the deformity was more common in the more active child. The relation to osteoarthrosis will require a prospective survey with a delay of at least a generation before the results are known.

Another pattern of osteoarthrosis is that associated with protrusio acetabuli. The relative frequency of this deformity in rheumatoid arthritis has led to the suggestion that unrecognized rheumatoid arthritis has preceded degenerative change (Murray and Jacobson, 1971), particularly if osteophyte formation is minimal. To date, there is little histological or serological support for rheumatoid arthritis being a cause of degenerative hip disease. Where characteristic rheumatoid changes are present elsewhere, *e.g.* in films of the hands and feet, the diagnosis of rheumatoid hip disease is reasonable. If not, caution should be exercised in making this diagnosis, based on protrusio acetabuli alone. Alexander (1965) has proposed that primary protrusio in adults, progressing as it may to osteoarthrosis, can result from stress during the adolescent growth spurt. A subsequent failure in pelvic remodelling, leading to protrusio, correlates with the female sex predominance, coxa vara and premature epiphyseal fusion.

---

*Reprints from Dr. D. J. Stoker, Institute of Orthopaedics, Royal National Orthopaedic Hospital, 234 Great Portland Street, London W1N 6AD.

Severe destructive change in the hips, often with radiological features of aseptic necrosis, may follow therapy with corticosteroids (Sweetnam *et al.*, 1960). It is rare for a patient with significant degenerative hip disease to escape treatment with either phenylbutazone or indomethacin. In a minority of those so treated, the accelerated progress of a destructive arthropathy suggests that the drug régime may be implicated (Arora, 1968; Allen and Murray, 1971).

These various starting points might suggest that osteoarthrosis is due to a mixture of inherited and environmental factors (Kellgren, 1961). Alternatively, a final common pathway may exist in what is most probably a multifactorial disease. However, so little is known about the detailed pathogenesis that these alternatives must remain unresolved. Most pathologists seem to be in no doubt that osteoarthrosis begins in the cartilage, although the nature of the process is obscure. It is claimed that the earliest finding is a characteristic splitting and fragmentation (fibrillation) of the articular cartilage. Byers *et al.* (1970, 1976a, b) have produced evidence from a study of cadaveric hips, which indicates that, in this joint, two classes of process affect the cartilage: (a) commonly occurring changes of limited progression not leading to deformity of the joint, and (b) less common progressive changes consistent with a disease process. In any event a destructive process leads to thinning of the cartilage layer, and eventually to focal exposure of subchondral bone. Whether such tissue response is due to fatigue failure of the collagen network (Freeman, 1975), when abnormal structural relationships could be implicated, to primary failure of the chondrocyte (*British Medical Journal*, 1976), or to some other mechanism is unknown. Hypotheses abound (Kempson *et al.*, 1975), including that the disease originates in bone or as a failure in joint lubrication. The proposition that osteoarthrosis is an arthropathy associated with the aging process has tended, in the past, to deter investigation into its aetiology. In more recent years, however, the study of genetic, endocrine, metabolic, vascular and biochemical factors has led to the accumulation of much data on the subject, particularly in respect of articular cartilage. Many questions remain unanswered. If osteoarthrosis is an aging process, why has age-correlated change not been demonstrated in non-articular hyaline cartilage? Why is involvement of the hip, knee and terminal interphalangeal joints of the fingers so common, yet involvement of the ankle and wrist relatively rare?

To the general radiologist, osteoarthrosis of the hip is a frequent finding during routine film reporting. Most patients with the condition show changes which are advanced on presentation. X-ray examination may reveal reduction of the joint (or cartilage) space, sclerosis of subarticular bone (eburnation) on both sides of the joint, and subarticular cystic change. Perhaps the outstanding feature which may lead the radiologist to diagnose degenerative change is the marginal osteophyte. However, Danielsson (1964), in a study of 86 patients where the diagnosis of osteoarthrosis was made solely on the presence of osteophytes, showed over the next 11 years only one patient who produced joint space narrowing. The remaining 85 patients exhibited no progressive radiological change. On this evidence and that of the pathologists, one is forced to agree that the earliest definable stage of progressive osteoarthrosis is narrowing of the joint space. But early loss of articular cartilage is often patchy or focal, and this usually precludes its radiographic demonstration. The width of the normal joint space varies from one subject to another, although in unilateral disease the width can be compared with the other hip, if that is presumed to be normal. The unequivocal diagnosis of narrowing requires a reduction by at least one-third in the width of the joint space (Gofton, 1971). The hip, being a ball and socket joint, presents a further problem because focal loss of articular cartilage nearly always occurs in the antero-superior quadrant, and in the earlier stages will only be shown in tangential (preferably weight-bearing) views. It therefore seems unlikely that the radiologist will be able to diagnose the early changes in articular cartilage observed by the pathologist.

Where does the radiologist now stand in the diagnosis of osteoarthrosis? He is unable to recognize the early disease, often unable to predict the symptomatic patient, but able to identify various patterns of joint disease (Gofton, 1971; Jeffrey, 1975), the significance of which is not always clear. More recently, attempts have been made to prove that osteoarthrosis is always a secondary disorder

(Stulberg *et al.*, 1975; Solomon, 1976). Solomon claimed that a predisposing abnormality was apparent in all but 27 of 327 patients with degenerative disease of the hip. Such correlation in excess of 90% is not within the experience of most practising skeletal radiologists, and leaves little room for the inclusion of other possible causes, such as disparity in leg length (Gofton, 1971). We must continue to observe critically the films of our patients with degenerative hip disease. All osteoarthrosis may be secondary, but proof will not come from subjective radiological impressions, but by future correlation of accurately observed diagnostic signs from clinical, radiological and pathological sources.

DENNIS J. STOKER

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Looking both ways

Presidential address delivered at British Institute of Radiology Annual Congress – 9th April 1976

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Department of Physics, Institute of Cancer Research, Sutton, Surrey

(*Received July, 1976*)

ABSTRACT

The address looks backward over the progress made in the techniques of radiology—both diagnosis and therapy—over the past 30 years and forward to the possibilities which lie ahead. It draws attention to the continuing need for basic research as the source from which practical advances spring, illustrating this from the development of radiosensitizing drugs. Finally, it emphasizes the importance of the Institute as an interdisciplinary forum in the present era of rapid technological advance.

Many years ago, when I was a young man, I used to look upon Presidential addresses to scientific societies as necessary evils—to be tolerated and, if short, applauded, but hardly enjoyed. One could not expect any new information but only reminiscence and anecdote. I have now had to look at the matter from a different point of view and I confess I find it hard to depart from the pattern I used to decry. However, when one spends most of the year wrapped up in one's own speciality, there is something to be said for taking a more comprehensive view of the whole field occasionally, and the Annual Congress provides an excellent opportunity of doing this, especially this year for there are many new ideas in the air. If I were to talk only about matters on which I have worked myself it is unlikely that this would interest more than a few. I propose instead to make a lightning tour of a large part of the field of radiology—both therapy, diagnosis and their supporting sciences—to see how far we have come in the past few decades and where we seem to be going. In speaking about today I shall be talking principally about the achievements of my younger colleagues and their hopes for the future. One of the compensations of taking on the grinding routine of heading a large department is that one can take as much pleasure in the achievements of one's younger colleagues as ever one may have done in one's own. I hope that by drawing on my own recollections for the past and on their work for the present and future I may be able to give an acceptable mixture of what is old and what is new. For I shall understand in the first place by my title the "arrow in time"—looking back and looking forward.

Many of you will remember the series of advertisements for a particular brand of petrol, which decorated our bill-boards in this country some years ago. In surveying where radiology has come from and where it is going to, I am struck by the same phenomenal speed of change—"That's it—that was!"

When I came into the field in 1942 the few physicists in medical work were either involved in teaching medical students or were attached to radiotherapy centres, and their principal, sometimes only, research activity was radiation dosimetry. In the M.R.C. Radiotherapeutic Research Unit which I joined, I remember we were using for dosimetry the Wulf string electrometer to measure the charge on small condenser ionization chambers (Fig. 1). This instrument must have been designed at least 30 or 40 years earlier but the chambers we were using were at least "air wall" and could measure what we would now call the "exposure" accurately in röntgens (Boag, 1956). I still find these chambers useful today though I have, alas, lost track of the Wulf electrometer. It was in these days, too, that Frank Farmer

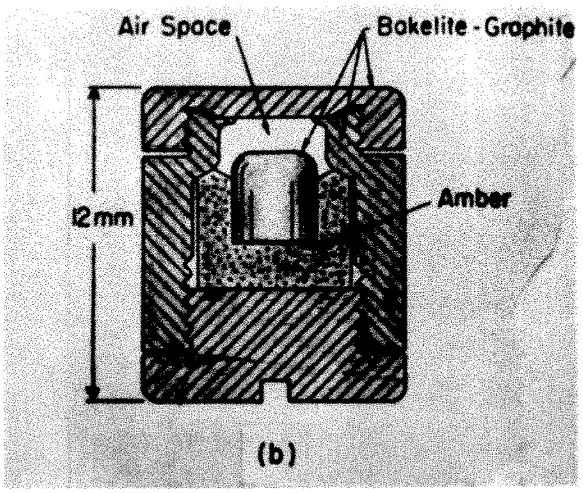


FIG. 1.

BD2 chamber designed by a group of physicists in 1944 and widely used.

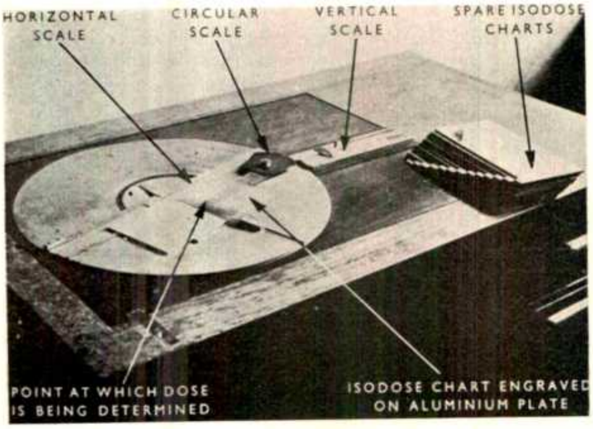

HORIZONTAL SCALE
CIRCULAR SCALE
VERTICAL SCALE
SPARE ISODOSE CHARTS
POINT AT WHICH DOSE IS BEING DETERMINED
ISODOSE CHART ENGRAVED ON ALUMINIUM PLATE

FIG. 2.

"Computer" for use with the 10 g Ra beam unit of the M.R.C. Radiotherapeutic Research Unit.

designed his simple and reliable new electronic circuit (Farmer, 1946) which has since, in developed form, become one of the principal measuring instruments in this country and in many others.

In those days deep therapy equipment generally operated at 200 to 250 kV and moist desquamation was the rule rather than the exception. The pioneer 1 MeV equipment (Allibone *et al.*, 1939; Phillips and Innes, 1938) which George Innes kept running virtually without "down time" for some 30 years, was the only supervoltage equipment in this country —unless one counts the few radium beam units of which we in the M.R.C. unit possessed one containing no less than ten grams of radium! We even had a simulator and a computer to go with it! (Wood and Boag, 1950). The simulator must have cost about £150 and the computer perhaps £100 (Fig. 2).

The few physicists in the field were, however, well aware of the potential of both Betatrons and Cyclotrons for radiotherapy and plans were being made for the clinical use of both these devices. We had designed an isocentric mounting for a betatron and were in conversation with the Metropolitan-Vickers company about this (Howard-Flanders and Newbery, 1950). However, two events changed this plan. A chance remark by someone who had been on a visit to the United States was one of these events. A medical man, he had nevertheless kept his eyes and ears open to scientific matters also, and he commented to us on his return that he had heard American scientists were thinking of accelerating electrons on radiowaves. This germ of the idea, coupled with the newly-available information on radar, was enough to start us thinking and Paul Howard-Flanders, together, later, with Dick Newbery, began working on a single-cavity standing-wave accelerator with the help of GEC Research Laboratories. The second circumstance was the fact, which came to light a few months later, with the formation by universities and other interested groups of the so-called "Accelerator Panel", that D. W. Fry and his team at T.R.E. Malvern were already working on a travelling wave linear accelerator and this, in due course, was so successful that the standing-wave design was abandoned (Fry *et al.*, 1948). The standing-wave principle has, however, been adopted within recent years in both the U.S.A. and Japan for small 4 to 5 MeV accelerators.

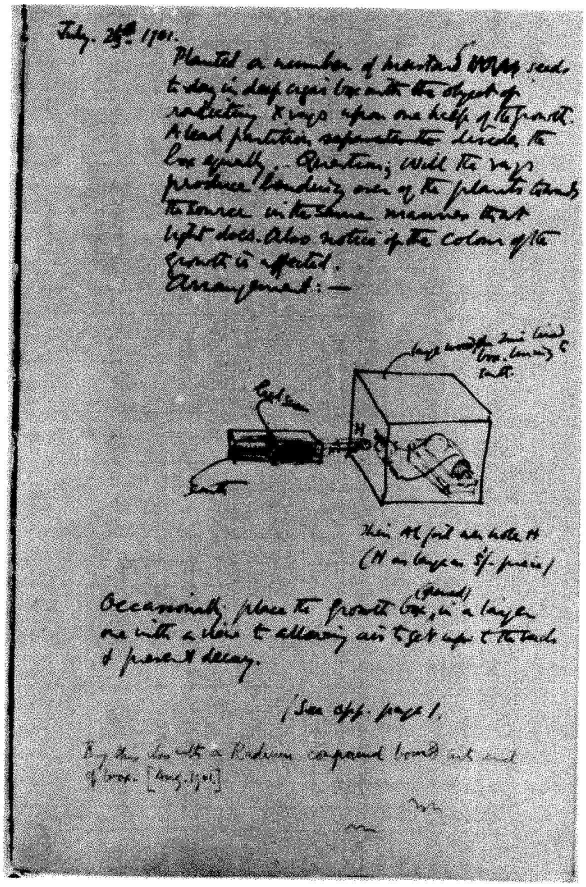
There were many other new ideas in the air at that time, too. When the synchrotron principle was proposed the first experimental verification of this was made by Goward and Barnes in 1946 at the Army laboratories in Fort Halstead after modifying a tiny 2 MeV betatron of Kerst's design which they had imported from the U.S.A. for radiography (Goward and Barnes, 1946). One other project which took rather longer to launch was neutron therapy. I was sent by the M.R.C. in the summer of 1949 to visit cyclotron establishments in the U.S.A. with a view to setting up a cyclotron for a trial of neutron therapy by Dr. Constance Wood, the Director of the Radiotherapeutic Research Unit, and for radiobiology studies by Dr. L. H. Gray, who was head of the basic research group. Plans were prepared and submitted in 1950 just in time to be caught by one of the first of our recurrent financial crises.

Let us now look the other way and see what has followed some 30 years later. Radiation dosimetry is no longer a main line of research but rather a routine activity which can be performed accurately and conveniently with very expensive commercial equipment. There is some danger in attempting to remove *all* the difficulties from a task such as this—the operator no longer has to stop and think so often, and may tend to lose sight of the basic principles when none of the design is his own.

Similarly the sophisticated treatment machines we use today are so easily controlled that they may seem to have almost reached the stage of the "safety bicycle", but the need for maintaining and, indeed, constantly improving safety in their use is even greater in view of their far higher output and penetration. In the very early days of "supervoltage" the choice of beam energy sometimes seemed to depend more on what the machine could be designed to attain than on the dimensions of the patient, but the few dinosaurs proved insufficiently adaptable and have vanished. Treatment planning, which was a rather tedious process in the dark ages, is now so highly automated (Bentley and Milan, 1972) and the beam profiles so much more under control, that almost any size or location of tumour in a patient can be treated—provided one knows where it is and how far it extends. Even the much more difficult problem of tailoring a fast neutron beam to the requirements of radiotherapy has been solved efficiently by the M.R.C. cyclotron team and the renewed interest in this form of radiotherapy is due largely to the encouraging clinical results which have been reported from the Hammersmith unit (Catterall, 1974).

However, I believe that those who devoted their time 30 years ago to planning and gradually bringing about these vastly-improved radiation facilities hoped from them more than they have as yet achieved in improved treatment results, and we have to enquire why this should be so. One source of error has been indicated in an earlier sentence—uncertainty about the precise location and extent of the tumour: this is a problem in diagnosis about which we shall have more to say later. But what of the varying responses of different tumours to identical irradiation régimes? This question brings us to radiobiology and we must first take a look backwards.

I well remember the excitement with which we awaited the publication of Lea's book (Lea, 1946). My own copy is dated on the day of publication—April 9, 1946. This book was undoubtedly a milestone on the way to a more scientific approach to radiobiology and has been recognized as such throughout the world. It contained the essence of virtually all the previous work on the radiobiology of living cells, distilled and clarified by the author's critical intelligence. It took as background the work of Dessauer, Crowther, Timoféeff-Ressovsky, Zimmer, Gray, Read, Spear and many others as well as Lea's own extensive experimental research. Perhaps you will allow one backward glance to an even earlier era. One of my predecessors at the Royal Marsden Hospital as well as in this Presidency was Major C. E. S. Phillips, and Fig. 3 shows a page from his laboratory notebook describing an X-ray experiment on the growth of mustard seedlings performed at the Royal Cancer Hospital, as it then was, on July 25 in the year 1901. He wished to discover whether the seedlings would bend over towards the source of X rays as they do towards a source of light. They didn't.



July. 25th 1901.

Planted a number of mustard [illegible] seeds to-day in deep cigar box with the object of radiating X rays upon one half of the growth. A lead partition separating the two divides the box equally. Question; Will the rays produce bending over of the plants towards the source in the same manner that light does. Also notice if the colour of the growth is affected.

Arrangement:—

Large wooden [illegible] lined box, [illegible]
[illegible]
Earth
[illegible] H [illegible] H
(H [illegible])

Occasionally place the growth box, (closed) in a larger one with a door to allowing air to get up to the [illegible] to prevent decay.

(See opp. page 1.

[illegible] Radium compound [illegible] [Aug. 1901]

FIG. 3.

A page from Major Phillips' laboratory notebook dated July 25, 1901, describing an early radiobiological experiment.

Lea's achievement in analysing and correlating the earlier work and in giving it a mathematical framework was immense. In his latest work, however, he recognized the vital importance of the hidden chemical stages in radiation action and had begun to equip himself for the chemical studies which he saw to be necessary for their elucidation before his tragic death in 1947. This takes us to even more basic studies.

In 1944 Joseph Weiss had published the seminal idea that radiation action in aqueous solutions was probably initiated by the radicals formed in water along the tracks of the secondary electrons and had indicated some of the consequences of this hypothesis (Weiss, 1944). For many years radiation chemists argued about the nature of these radicals and the reaction mechanisms involved. One could argue interminably about the mechanism of a sausage machine into which meat and many other ingredients enter at one end and finished sausages come out at the other. So it was in these days, when the radiation chemist could determine only his initial products and his final products, but not the radiation-induced reaction pathways which connected them. His fastest time-scale was measured in minutes, or at best in seconds. If we glance the other way we now find that radiation chemists, by using the intense radiation pulses from a linear accelerator and identifying reactants by their optical absorption spectra, can study reaction kinetics routinely on a microsecond time-scale; with some difficulty on a nanosecond time-scale; and in at least a few centres on a picosecond time-scale (*i.e.* in a few millionths of a millionth of a second) (Adams *et al.*, 1975). It is worth noting that the entry into this fast reaction field was made largely, though not entirely, by physicists and chemists working in radiotherapy centres—because they were fortunate enough to have access to pulsed linear accelerators, machines not then available to academic radiation chemists. I doubt whether research of an equivalent "look-see" nature would readily be funded today, for no-one could say with any certainty that the techniques would be successful, let alone whether anything important would come out of it. True, physical chemists had shown what could be done with visible light (Porter, 1950) and pulse radiolysis using the electron pulses from a linear accelerator seemed worth trying. The concentration first was on simple chemical solutions, so remote from any apparent application in radiotherapy that one was able to pursue the research quietly and thoroughly. Progress in research, however, requires not only time for reflection but also a high component of plain luck. It was fortunate that at least one of the important radical species formed in water by the radiation pulse was very highly coloured and therefore easy to follow by optical methods. It looked deep blue—that is to say, it strongly absorbed red light. This new radical species was the "hydrated electron" (Hart and Boag, 1962; Keene, 1963) and it proved not only a popular toy for radiation chemists but also an important key to understanding the mechanism of radiation-induced reactions in aqueous solutions (Boag, 1965).

Those of you who are unfamiliar with this part of the field may find it easier to understand what is meant by a hydrated electron if I show a simple model of this species (Fig. 4). The electrons knocked out of ionized water molecules do not immediately attach themselves to other water molecules to form negative ions, but instead wander for some time among them. Now a water molecule has an "electric moment" which causes it to align itself in any external electric field. We can simulate such molecules by floating discs each carrying an embedded magnet which will respond to an external magnetic field. If we now swing another magnet above this assembly to represent a wandering electron, we find that as long as it moves rapidly the inertia of the moving discs prevent them from turning to follow its motion. As the moving magnet slows down, however, they begin to respond and ultimately the moving magnet is "captured" by the ordered assembly of molecules which it has itself created. It remains mobile, but much less so than before, since its movements are now impeded by the inertia of its captors which must turn to preserve the same radial configuration. This is a two-dimensional model of an electron trapped by its own hydration shell of oriented water molecules—the transient species christened "hydrated electron" in 1953 by Platzman, and the simplest of all negative ions in solution.

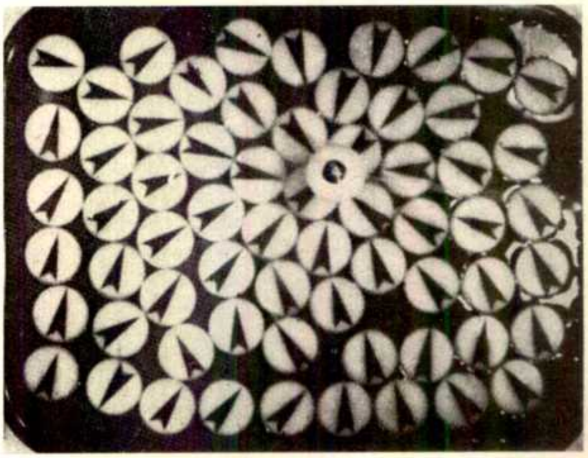


FIG. 4.

Model of the hydrated electron. Floating wax discs with embedded magnets cannot respond to a rapidly swinging magnet, but as it slows down they align themselves and trap it at the centre of their configuration.

Let us see now where we are today in radiobiology. A knowledge of the kinetic mechanisms of many simple radiation-induced reactions has led chemists to a study of much more complex systems. It has become possible, not only to *understand* the initial chemical stages of radiation action about which Joseph Weiss speculated so fruitfully some 35 years ago, but also to *intervene* at this early stage and successfully modify the final effect whether this be a chemical or a biological change. One does this by introducing into a solution, or a living cell, substances which we call either "protectors" or "sensitizers" according to their action in reducing or enhancing the final effect considered.

The sensitizing effect of dissolved molecular oxygen, known by some very early workers, had been rediscovered by Read and Thoday in the late 1940s and its significance for radiotherapy was at once

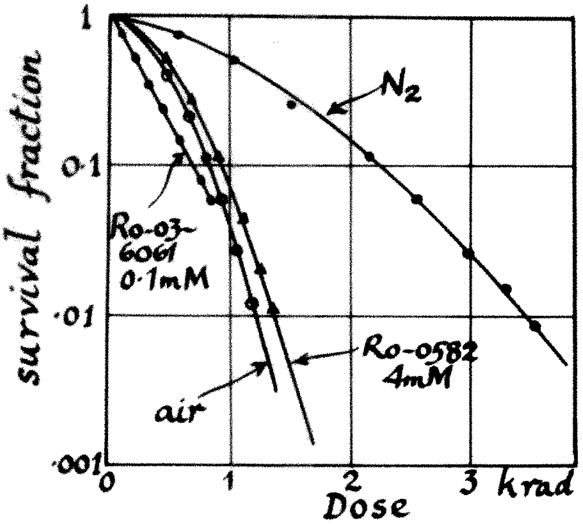


Fig. 5.

Cell survival curves for mammalian cells irradiated in suspensions equilibrated with nitrogen, air, or nitrogen plus either of two sensitizers. The biradical Ro–03–6061 at 0.1 mM concentration has an even greater sensitizing action than oxygen and has removed the initial "shoulder" of the curve (Cooke *et al.*, 1976).

recognized by Gray (Gray *et al.*, 1953). Any pockets of anoxia within a tumour can protect viable cells within them to an extent which is equivalent to reducing the radiation dose by a factor of nearly three. The particular agents of most interest to radiotherapists at the present time are, therefore, the sensitizers which mimic oxygen in sensitizing effect but are not themselves rapidly metabolized by cells. Such substances can diffuse further from capillaries than can oxygen and thus, it is hoped, they may reach all parts of the anoxic regions. One such substance—Ro 0582—developed by Adams and colleagues at the Gray Laboratory (Asquith *et al.*, 1974) in collaboration with Roche Products Ltd., has now been cleared for clinical trials (Fig. 5). Another promising substance discovered by Cooke *et al.* (1976) at the Institute of Cancer Research and still at the laboratory stage, shows a particularly interesting property—it gives enhanced sensitization at low radiation doses, greater even than oxygen itself. It does this by removing the "shoulder" from the survival curve, leaving it as a simple exponential. This may be due to an interference with repair mechanisms. If this property can be preserved in a clinically usable drug, the latter should be effective in conventional fractionated radiotherapy.

Now the principal rationale of practically all the proposals at present under consideration for improving the results of radiotherapy—fast neutrons, pi-mesons or charged particle beams from enormous accelerators—is the elimination of the protective effect of anoxia. When faced with alternative methods of doing this we must consider very carefully their relative costs and whether, if successful, they might become generally available. The anoxic sensitizer approach stands up well to this examination. The world can doubtless afford one or two experimental pi-meson facilities, from which we may learn something of basic interest, not necessarily because of the mesons but perhaps because of the high calibre research team assembled to use them. But if mesons can be afforded, then adequate support should not be denied to other less expensive but no less promising schemes.

The British Institute of Radiology, however, has always had a preponderance of diagnostic radiologists in its ranks and I have been talking thus far about radiotherapy and radiobiology. One of my early remarks may not have passed unnoticed, however. I said that with modern equipment treatment plans can be prepared to irradiate adequately almost any tumour provided we know its location and extent. This is a problem in diagnosis and I should like to turn now in that direction. I cannot reminisce on the subject of diagnostic radiology because it is only a few years ago that I began to dabble in this field myself, and I should like to weight my remarks on this subject more to the future than to the past. My enigmatic title "Looking Both Ways" can be interpreted not only in terms of the arrow in time but also as indicating a choice of alternative imaging techniques, and the diagnostician today is, indeed, offered a wide choice. I shall take just one backward glance for in trying to educate myself in this subject I have been driven back to the original papers of Röntgen himself and a few others of that era. In these days of Xerox copying it is very easy to obtain the text of the full English translation of Röntgen's papers, the first of which appeared in *The Electrician* in January 1896, only three weeks after his original communication to the Wurzburg Electromedical Society (a copy of which we have in the Institute's library). It is a model of scientific writing. The fluorescence, the photographic effect, the ionization of air and much else were all set out clearly in these first two papers. On February 15, 1896, three weeks after *The Electrician* published Röntgen's first paper, Major C. E. S. Phillips, to whose radiobiological experiments I have already referred, was taking quite satisfactory X-ray pictures of simple objects at the Royal Cancer Hospital (Fig. 6). It usually takes a little longer to follow a lead today.

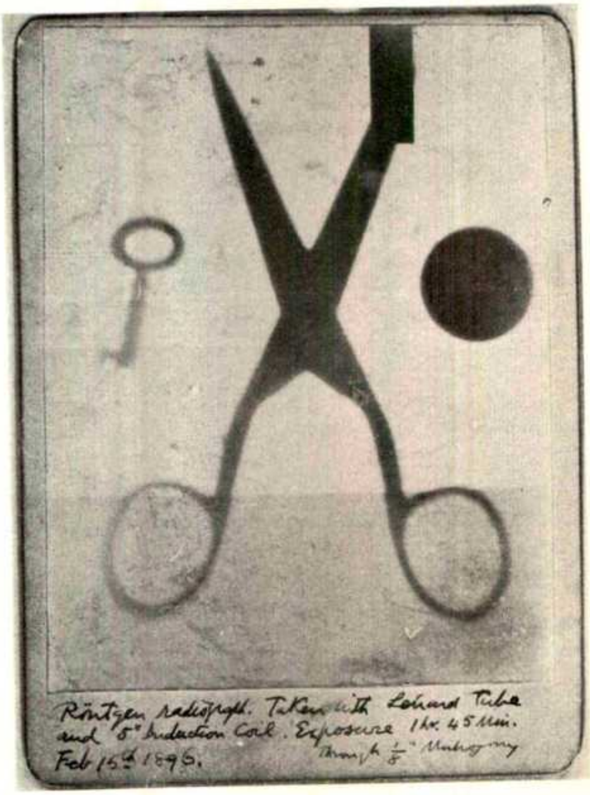

Röntgen radiograph. Taken with Lenard Tube
and 5" Induction Coil. Exposure 1hr. 45 Min.
Feb 15th 1896.
Through 1/8" Mahogany

FIG. 6.

The earliest surviving radiograph taken by Major C. E. S. Phillips at the Royal Cancer Hospital is dated February 15, 1896—three weeks after Röntgen's paper was published in *The Electrician*.

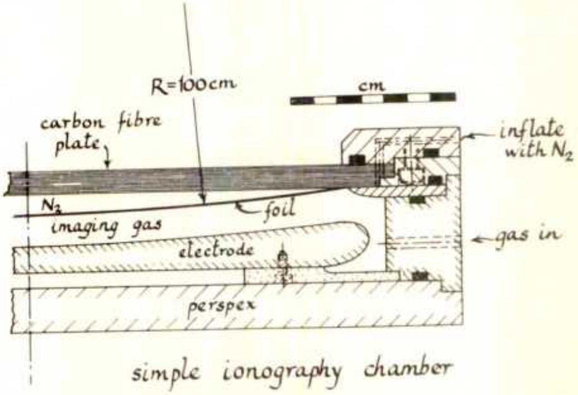


FIG. 7.

Prototype ionography chamber used in developing the technique.

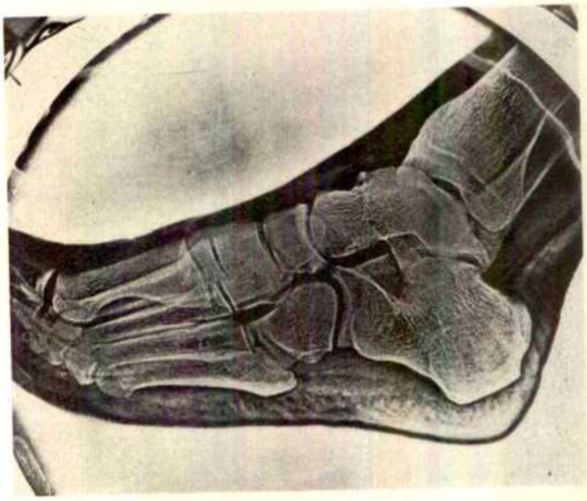


FIG. 8.

Radiograph of the author's foot taken on the chamber of Fig. 7.

During the past few years I have been exploring some new ways of forming X-ray images, among them ionography—that is, the formation of the latent image as a distribution of electric charge on an insulating foil and its subsequent "development" by immersion in a cloud of electrically-charged powder (Boag, 1975; Johns *et al.*, 1974). In previous talks on this matter I have been accustomed to acknowledge the early work of Augusto Righi of Bologna, who published a small booklet in 1905 containing a crude "ionograph" of a hand (Righi, 1905). However, I was more than a little surprised to discover a few months ago that Silvanus Thompson, whose name is well-known in this Institute as the first President of what was then the Röntgen Society, demonstrated ionography on May 8, 1896 in a discourse delivered at the Royal Institution of London. The experimental set-up was rather crude and the picture is not a good one but the germ of the idea was there.

Let us now look at a modern prototype ionography chamber and at some of the pictures it yields (Fig. 7). The X-ray beam deposits some 50% of its energy by absorption in a thick layer of high-pressure gas. The ions produced in the gas are collected on a plastic foil, there to form the invisible "latent image". After removing the foil from the chamber and immersing it in an aerosol of charged particles this latent image becomes visible (Fig. 8). Ionography is inherently an efficient process which should rival in sensitivity the use of film with intensifying screens. I cannot predict to what extent, or how soon, it may compete seriously with the silver emulsion but it is now sufficiently acceptable both in resolution and in sensitivity to be considered a competitor, and at least one determined attempt is being made to achieve a commercial equipment in spite of the somewhat formidable engineering difficulties (Proudian *et al.*, 1974).

Electrostatic methods of image formation are, of course, already well established in xeroradiography. The pictures which this method of imaging yields are of particular interest in soft-tissue radiography where the contrast differences are normally small and the pictures benefit from the edge enhancement which can be produced. Xeroradiography is likely to find a permanent place, too, in vascular studies or lymphography since it allows one to follow the path of vessels even where they lie behind strongly absorbing bone. Its latitude allows the soft tissue structure and the bony structure to be examined on a single picture. The methods for laying down the electrostatic latent image, whether solid state or gaseous, are already very good. Not enough has been done yet in exploring new ways of rendering this latent image visible, and it may well be in this direction that we shall see a further development of this particular imaging system.

The most exciting new way of looking at the internal topography of the patient which has been added to the repertoire of the radiologist for many years is computerized axial tomography (Hounsfield, 1973). This brings me to a very basic difference between today and yesterday. Today we have at our command an extraordinary power of computation and there seems hardly any limit, except that imposed by quantum statistics, to what can be done in the electronic processing of pictures by modern digital computer techniques. It is to the application of computer power that we owe both the CT scanner and some of the striking new developments in ultrasound which I shall illustrate presently. X-ray pictures hitherto have been shadowgraphs—a little better than silhouettes but essentially a composite addition of many silhouettes superimposed one upon another. Conventional tomography with moving tube and moving film attempts to sharpen the shadows from one plane and smooth out those from other planes, and remarkable ingenuity has been employed in doing this, not without success. The quite new thing, however, about the CT scanner is that it presents detailed information about the nature of the tissue at each point in the picture, unencumbered by shadows from other parts of the object. In looking at the resulting pictures we seem to be turning the pages of *Gray's Anatomy* once again (Fig. 9). Here, surely, must be one way of determining more accurately the exact position and extent of any tumour and thus allowing precision treatment planning to be used effectively. Are we then to abandon all other methods of exploring the internal organs and concentrate entirely on this new and exciting technique? Hardly, I think. It has its own unique advantages and it must be available for those special procedures where it has no rival, but economic factors are not unimportant and, as in radiotherapy so in diagnosis, we must make a determined effort to simplify and reduce the cost of these new and powerful techniques so that they may be more widely applicable, or else to find alternative less expensive ways of obtaining the necessary diagnostic information.

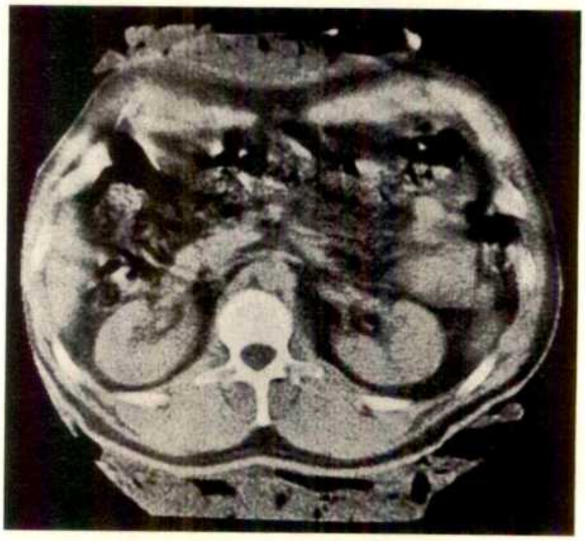


FIG. 9.

Computerized axial tomogram taken on the EMI whole body scanner. (Courtesy of EMI Medical Ltd.)

Ultrasound is one of these alternatives which is already on offer, and which is in a phase of rapid growth and development. At the power levels used for diagnosis it is non-damaging and can provide high-resolution tomograms, with the structural features of the tissue or organ imaged primarily by their elastic response to the ultrasound pulses. It may therefore be expected to give information which is different from that given by X rays but which will often be quite as valuable for diagnosis (Fig. 10). We shall sometimes wish to *look both ways*. By utilizing both the storage and the analytical power of a small computer, however, one can do a great deal more with the reflected ultrasound pulses than merely record their transit times and hence plot out the positions of reflecting interfaces in the single plane scanned. That has been the classical approach. But the computer can store in its memory the pulses reflected from many different planes and can retrieve them on demand, with the pulses sorted according to amplitude as well as transit time. In due course, we may, therefore, expect to see a 3D picture

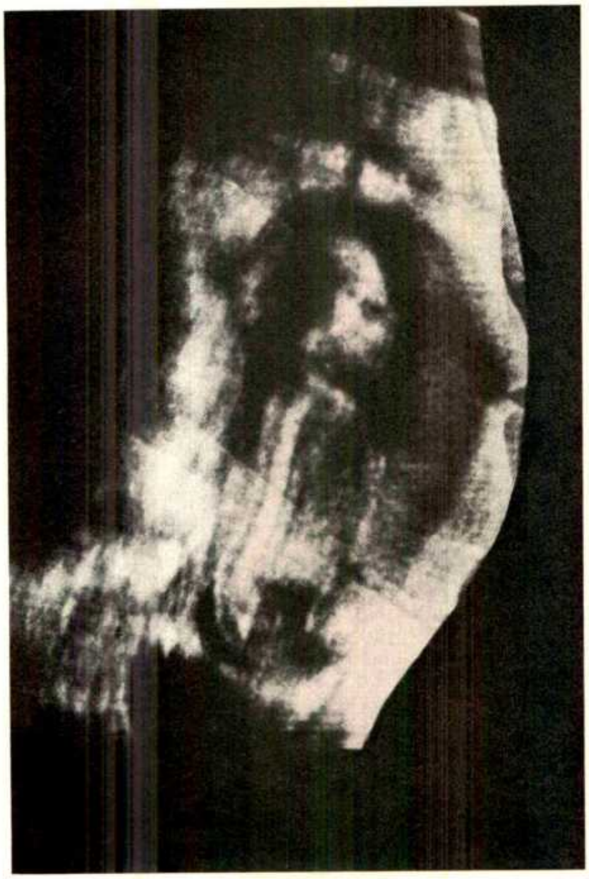


FIG. 10.

Ultrasound scan of fetus in the womb. (Courtesy of Dr. D. H. Rose, Royal Marsden Hospital.)

reconstructed from a single ultrasound scan through the region of interest in the patient, with a grey scale derived from the pulse amplitude variation.

Another new possibility with ultrasound is concerned not with imaging *per se*, but with recognizing tissue type—a kind of remote histology or histopathology (Nicholas and Hill, 1975). Due to the diffraction of the sound by the regular structure of tissue there is a variation in the signal strength with the angle between ingoing pulse and orientation of the detector. The frequency of this angular variation is characteristic of the type of tissue in the region examined. Such tissue recognition patterns may be compared with the manner in which the X-ray CT scanner identifies different tissues by their X-ray attenuation properties, or, more fundamentally, in terms of electron density and atomic number. The equipment for ultrasound exploration is likely to be an order of magnitude less expensive than the X-ray CT scanner as well as incurring no radiation exposure.

I have referred more than once in this survey to the very high cost of some of the powerful new techniques which are being explored today in both therapy and diagnosis. It is worth emphasizing again that we must find the right way of evaluating these techniques, not merely substituting them for existing methods where the latter are already adequate. However, if we are to avoid using steam hammers to crack nuts we must ensure that entirely adequate nutcrackers are available or, if not, we must invent them. The "steam hammers", if you will pardon the metaphor, can then be reserved for the patients who really need them.

Finally, one can *look both ways* at The British Institute of Radiology. Beginning as the Röntgen Society in 1897, it has been a forum for the communication and discussion of all new developments in both diagnostic and therapeutic radiology since then. I do not, of course, make any chauvinistic claim that all the new developments have occurred in this country; simply that the B.I.R. has fostered, stimulated and informed the radiological community in this country and, by its publications, throughout the world, and has won an enviable reputation as a meeting ground for medical radiologists, scientific research workers, radiographers, and, last but not least, the engineers and industrialists who provide the tools with which we work. To survive as long as this with undiminished vigour the Institute has had to be adaptable, and to allow—indeed encourage—the emergence of special interest groups. The fact that such groups, which had their origins in the B.I.R., have, in several instances, become fully independent bodies, does not diminish the need for the original parent with its all-embracing membership to provide the meeting ground on which the different specialists can interact and co-operate, for it is in this way that advances in radiology are made and consolidated.

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The value of urography following lymphography in malignant diseases

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ABSTRACT

The need for urography following ascending pedal lymphography in malignant disease has been studied in 298 consecutive patients. Forty per cent of the urograms were abnormal. Urographic abnormalities due to the disease being investigated were heralded by abnormal lymphography except in four patients, three with carcinoma of the bladder and one with carcinoma of the cervix. The majority of abnormalities unrelated to the disease being investigated were of no significance. In a small number there was congenital malposition of the kidney so that it fell within the proposed field of treatment.

It is concluded that it is unnecessary to do routine urography with every lymphogram. Indications for urography are abnormality or suspected abnormality of the lymphogram, failure to locate the kidneys on plain films and clinical indications such as carcinoma of the bladder or carcinoma of the cervix.

Lymphography is a direct method of demonstrating abnormalities in the para-aortic and pelvic lymph node chains. Excretion urography and inferior vena cavography are indirect methods of demonstrating glandular enlargement when it is gross (Baum *et al.*, 1963; Brower and Seale, 1974). The combined use of these complementary techniques increases the accuracy of diagnosis in retroperitoneal disease (Hliniakowa *et al.*, 1972; Hopf and Fuchs, 1970; Lee *et al.*, 1964; Wilson *et al.*, 1965; Schwarz *et al.*, 1965; Masselot *et al.*, 1971), particularly when it involves the high para-aortic nodes. The indications for urography following lymphography are not universally agreed. In some centres, urography is omitted when the lymphogram is normal (Abrams *et al.*, 1965), while in others it is performed routinely following all lymphograms (Macdonald, 1973). In addition to being time-consuming and expensive, excretion urography is unpleasant for the patient, and carries a small risk of untoward reaction (Davies *et al.*, 1975).

Two hundred and ninety-eight consecutive lymphograms have been studied to determine whether the need for urography can be predicted from the lymphogram.

PATIENTS

The patients presented to the United Bristol Hospitals with malignant disease between January 1966 and June 1974. One hundred and ninety-five patients, aged seven years to 73 years had reticulosis, 117 being males and 78 females. One hundred and three patients, aged ten years to 88 years, had other forms of malignancy, 69 being males and 34 females (Table I).

TABLE I

CLINCAL DIAGNOSES OF PATIENTS

		Total number	Male	Female
Lymphoma	195			
Hodgkin's disease		136	83	53
Lymphosarcoma		21	13	8
Reticulosarcoma		18	10	8
Follicular lymphoma		12	5	7
Uncertain lymphoma		8	6	2
Male genital tract	45			
Seminoma		30	30	
Teratoma		12	12	
Lymphoma of testis		3	3	
Female genital tract	22			22
Urinary tract	7		6	1
Other sites	29		18	11
Total	298		186	112

METHODS

Conventional lymphography was done in all patients and included films taken at two hours and 24 hours. High dose urography was then done without ureteric compression.

From study of filling and 24-hour films, the lymphograms were classified into normal, abnormal or equivocal, without referring to the urograms.

The kidneys were recorded as visible in the 24-hour film when there was no doubt about their site. Abnormalities of the urograms were then recorded.

RESULTS

In 76 cases (26%) the lymphograms were normal and in 222 (74%) cases the lymphograms were abnormal or equivocal (Table II).

Sixty-eight patients (22%) had a total of 84 abnormalities of the urinary tract related to the disease being investigated (Table III). Five of these patients had normal lymphograms, associated with bladder carcinoma (3) or renal displacement by enlarged spleen or enlarged liver (2).

A further four of these patients had equivocal lymphograms at the initial examination. Two of them had minor ureteric displacement and their lymphogram became abnormal on follow-up. The other two had carcinoma of the cervix (1) and carcinoma of the bladder (1) and their lymphograms were finally judged to be normal.

TABLE II

RESULTS OF LYMPHOGRAPHY AND UROGRAPHY

Lymphogram diagnosis		Number with related abnormality on urogram
Normal	76	5
Definite reticulosis	117	41
Equivocal reticulosis	46	2
Definite metastases	31	18
Equivocal metastases	28	2
Total	298	68

Fifty-four patients (18%) had urinary tract abnormalities that were not caused by the disease being investigated (Table IV). Thirty-seven (12%) of these had acquired abnormalities of which prostatic hyperplasia (24 cases) was the commonest. The other 17 (6%) had congenital abnormalities, one having a pelvic kidney which was elevated surgically later in order to remove it from the proposed field of radiation.

Unilateral lymphograms

In 24 patients already described, only one foot was cannulated, either because of technical difficulties or because chest disease precluded simultaneous bilateral examination. Fourteen of these had abnormal lymphograms. Three of them had ipsilateral urographic abnormalities; two had contralateral ureteric abnormalities and nine had normal

TABLE III

RELATED ABNORMALITIES ON UROGRAPHY

Lymphogram diagnosis	Reticulosis		Other malignancies		Normal
	Abnormal	Equivocal	Abnormal	Equivocal	
Kidneys					
Probable infiltration with reticulosis	5	0	0	0	0
Displacement by spleen	5	0	0	0	2
Displacement by liver	0	0	0	0	1
Displacement by opacified nodes	4	0	0	1	0
Displacement by non-opacified nodes	1	0	1	0	0
Reduced renal function	1	0	2	1	2
	16	0	3	2	5
Ureters					
Displacement by opacified nodes	23	2	2	0	0
Displacement by non-opacified nodes	4	0	5	0	0
Displacement by opacified and non-opacified nodes	2	0	1	0	0
Ureteric obstruction	0	0	5	0	1
Displacement and obstruction	1	0	0	1	0
	30	2	13	1	1
Bladder					
Compr. by opacified nodes	3	0	0	0	0
Compr. by non-opacified nodes	2	0	1	0	0
Compr. by opacified nodes and invasion by tumour	0	0	1	0	0
Carcinoma of bladder	0	0	0	1	3
	5	0	2	1	3
Total abnormalities	51	2	18	4	9
Patients with more than one abnormality	10	0	0	2	4
Total patients	41	2	18	2	5

TABLE IV

CO-INCIDENTAL ABNORMALITIES ON UROGRAPHY

Nature of abnormality	Number of urograms
Kidneys	
Absent kidney: congenital	1
nephrectomy	1
Horseshoe kidney	2
Pelvic kidney	1
Duplex systems	5 (bilateral in 2)
Primary pelvic hydronephrosis	6
Simple cysts	5 (bilateral in 1)
Chronic pyelonephritis	6 (bilateral in 2)
Chronic pyelonephritis in a duplex kidney	1
Ureters	
Congenital hydroureter	1
Ureterocoele	1
Prostate	
Hyperplasia	24
	54 (total)

urograms. Ten cases had normal lymphogram and urogram.

Renal position and radiotherapy

One hundred and ten patients had abdominal radiotherapy. In 55 of these both kidneys were seen on plain radiographs; in 18 only one kidney was seen and in the remaining 37, neither kidney was seen.

DISCUSSION

The relatively high yield of urographic abnormalities (40%) seems to justify routine urography following lymphography. However, a study of the influence of these abnormalities on treatment shows that this is not so, and that the most important indication for urography is an abnormal lymphogram.

The precise details of treatment régimes are too complex to be discussed here, but in general, as retroperitoneal malignant disease becomes more extensive, alternative régimes, including chemotherapy as well as radiotherapy, may be used. The value of urography in this context is to show that the abnormality is more extensive than suspected. Renal infiltration with reticulosis is important because it is suspected only on urography (Schwarz *et al.*, 1965), but it is uncommon, and in the absence of lymph node abnormality it is extremely rare (Gowing, 1974). Other upper urinary tract abnormalities are due to either displacement or obstruction of the ureters. In the present series the demonstration of these complications did not alter the short-term management of the patients because the underlying lesions were shown on the lymphograms of all except four patients. These exceptions had carcinoma of the bladder (3) or carcinoma of the cervix (1), and these diseases are indications for urography. When there is ureteric obstruction, urographic assessment forms a baseline for following progress after treatment and its value is augmented by serial renography (Britton and Brown, 1969). The abnormal urograms in two patients with reticulosis, whose equivocal lymphograms later became abnormal, emphasize the value of urographic information when the lymphogram is equivocal.

Displacement or infiltration of the bladder were heralded by an abnormal lymphogram except in carcinomas of the bladder, in which urography is clinically obligatory.

The majority of coincidental abnormalities (Table IV) have no influence on management. The incidence of unsuspected chronic pyelonephritis is small and the possibility of diagnosing it does not justify routine urography. The most significant of the coincidental abnormalities are congenital abnormalities of position which lead to the kidneys lying in the fields of proposed radiotherapy (Table IV). It is debatable whether slight displacement of the kidneys from their expected positions is important, but major displacement can be, and was especially so in one patient who had a pelvic kidney that was elevated surgically before treatment began. Horseshoe kidney is important because its isthmus lies across the field of radiation to the para-aortic lymph nodes. In fact the majority of kidneys can be located on plain films, and urography is needed only when this cannot be done. Ultrasonic localization (Covington and Buzzi, 1972), and isotope localization (Sanders *et al.*, 1974) are alternative methods of renal localization that are not yet widely used.

Urinary tract abnormalities were commoner and more severe among patients without reticulosis than among those with reticulosis (Table III), but when the lymphogram was normal there was no significant urinary tract abnormality in either group, and urography is unnecessary.

The estimated additional cost of materials for post-lymphogram urography is about £5 and it is satisfying to advocate a radiological practice that saves money even though the annual saving is likely to be relatively small in most radiology departments.

CONCLUSIONS

It is unnecessary to do routine urograms with every lymphogram. The indications are:

(a) Abnormality or suspected abnormality of the lymphogram, either initially or at follow-up. The yield of urinary tract abnormalities is likely to be less in the reticuloses than in other malignancies.

(b) Failure to locate the kidneys on plain films when location is clinically necessary.

(c) Clinical indication for urography, including carcinoma of the bladder or cervix.

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Book review

"Trauma" and "No-Trauma" of the Cervical Spine. Ed. K. R. Kattan, pp. xi × 312, illustrated, 1975 (Illinois, Charles C. Thomas), $24.50.

I think it was Fleischner who said that a radiologist only sees what he looks for and only looks for what he knows. Nowhere is this dictum more pertinent than in the examination of cervical spine injury where the uninitiated can easily miss or misinterpret quite severe trauma. Experience is usually hard won but in this slim volume the wisdom of a lifetime is available to us all.

There are 11 authors, mainly based in Cincinnati, several of whom are household names in bone and joint radiology, but the ten chapters are not simply a collection of individual monographs. Dr. Kattan, who is modestly described as the editor, has contributed to each chapter. He has succeeded in blending the contributions of the several authors into a coherent whole, resulting in a very even style so that the reader would not suspect multi-authorship. What is greatly refreshing in an American book is the beautiful economy of words. Chapter 2 gets off to a bad start with references to "biomechanical mechanisms that produce pathologic insult to the human body" but such lapses are few and the tenor of the book is a concise, almost terse, down-to-earth description of types of injury, radiographic techniques and film-interpretation, and is mercifully free of trans-Atlantic polysyllabic wooliness. It is of similar size to Penning's book with which it inevitably has a lot in common, but it is probably of even greater immediate value on the reporting bench of an accident department, mainly by virtue of its wealth of illustration. Two-thirds of its 300 pages are devoted to radiographs of remarkably good quality when one considers the circumstances in which many of them must have been taken. It is on this feature, particularly, that the editor is to be congratulated; the collection and selection of hundreds of examples from all the contributors must have been a daunting task.

Not only is this book a "must" for all trainees, it is positively dangerous not to read it! It should be in every departmental library and regularly read by all students of radiology up to retiring age.

J. T. Patton

1977, *British Journal of Radiology*, *50*, 97–100

The "magnification sign" of triple mandibular fracture

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ABSTRACT

A new sign which can be readily detected in a standard postero-anterior projection of the mandible is described. It indicates that there are fractures of both mandibular necks and the horizontal ramus near the mid-line. There do not appear to be any situations in which a false positive sign is produced.

Fractures of the mandible are often difficult to detect. They have a habit of being hidden in one projection even when obvious in another. Because the mandible, like the handle of a bucket, is a rigid structure and because it is connected to the skull by a firm joint at each end, it commonly behaves as if it were a complete bony ring (Trapnell, 1967). If it always reacted in this way, fractures in it would always be multiple. In fact an isolated fracture can occur, probably mostly because of the mobility permitted in the temporomandibular joints. However, double and triple fractures are common and should always be sought when one fracture is found. The "magnification sign" is a valuable signal indicating that three fractures are present. It would be both dangerous and foolish to make such a diagnosis on the evidence of any one projection only. The presence of three fractures indicated by the magnification sign must be confirmed by other appropriate projections.

THE MAGNIFICATION SIGN

The essence of the sign is that the mandible appears "too wide" for the upper jaw—hence the term "magnification sign". It is best demonstrated in a standard postero-anterior projection of the mandible. Two factors contribute to the production of this appearance. First, the two angles of the mandible are abnormally widely separated from each other and the ascending rami and the part of the horizontal ramus attached to them are "opened out". Second, as a result of the first, the mandibular molar teeth are displaced lateral to their corresponding teeth in the upper jaw (Figs. 1, 2, 3 and 4). In assessing this second component of the sign it is important to make sure that like is compared with like—*i.e.* that the position of lower eight is related to the upper eight and not, for example, to the upper six.

Since the mandible normally behaves as a rigid structure it is clear that the angle of the mandible on

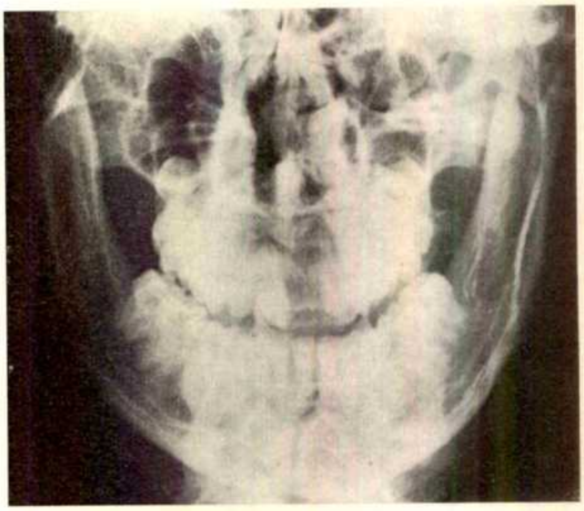


FIG. 1.

The "magnification sign". The lower jaw appears too large for the upper jaw. There are fractures of both mandibular necks, allowing medial angulation of both mandibular heads and lateral displacement of both ascending rami, and a fracture of the horizontal ramus near the mid-line.

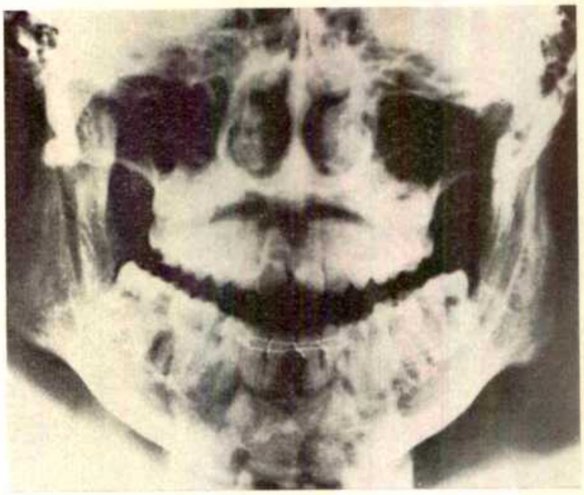
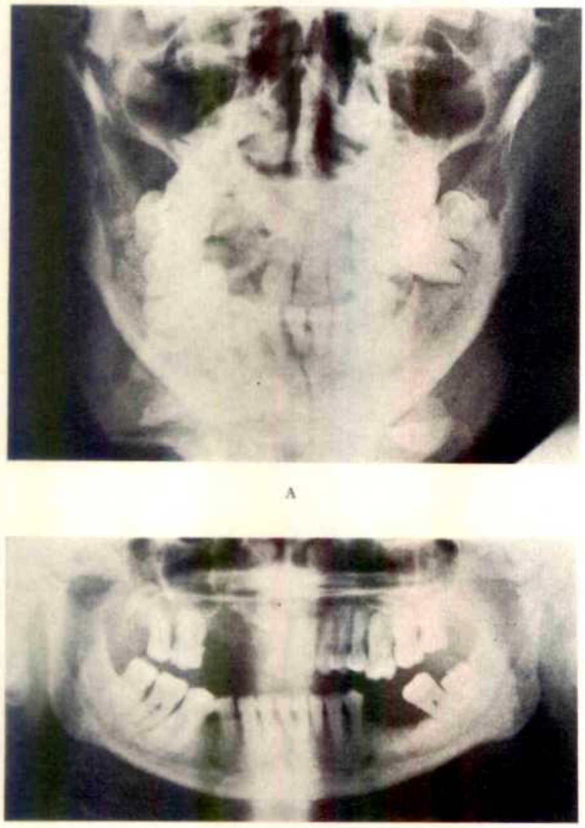


FIG. 2.

Another case of triple fractures showing magnification (after wiring of the mid-line fracture). Note the "opened out" appearance of the ascending rami.



A

B

FIG. 3.

(A) Postero-anterior radiograph showing the "magnification sign" due to triple fractures.

(B) Orthopantomograph of the same patient showing the fractures of the mandibular neck on each side and a horizontal ramus fracture near the mid-line.

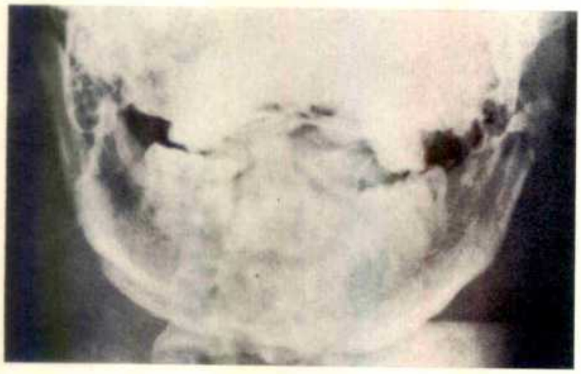


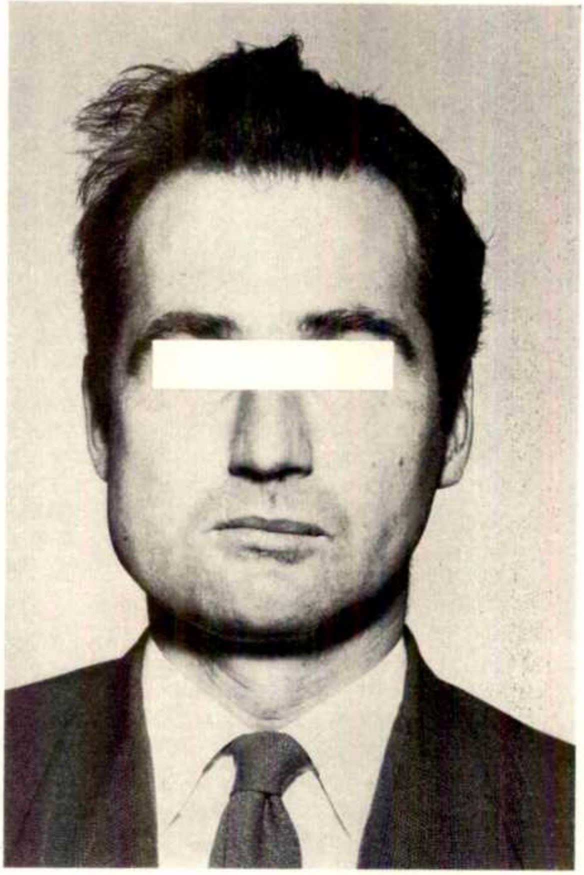
FIG. 4.

Triple mandibular fractures producing the "magnification sign" in a patient who also had a Le Fort III facial fracture. The "step" in the level of the mandibular teeth was not due to displacement of the teeth themselves but to the horizontal ramus fracture.

each side can only be displaced laterally, carrying the teeth with it, if (1) there are fractures of both mandibular necks (thus effectively disconnecting the mandible from the skull base), (2) there is a third fracture somewhere in the (otherwise rigid) horizontal ramus, usually near the mid-line.

Thus, for example, the commonly associated fracture of the neck of the mandible on one side and of the angle on the other could not produce the displacement necessary to produce the sign. Equally, fractures of both mandibular necks without a third fracture could not cause it either, since no "opening out" of the mandible is possible. My experience in ten patients exhibiting this sign has confirmed what theory suggests—that only a triple fracture of the kind described above will produce this appearance.

In acute cases soon after the injury there is often so much facial swelling that the presence of the

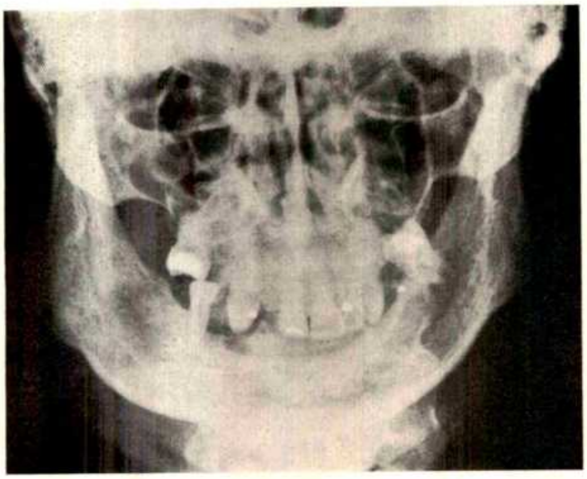


[redacted]

A

FIG. 5.

(A) A patient several years after proven triple mandibular fractures. Note the prominence of the mandibular angles, particularly on the right.



B

FIG. 5.

(B) Postero-anterior radiograph of the same patient. "Magnification" is clearly still present even though the fractures are healed and some teeth are missing (making exact comparison of the upper and lower molars impossible).

underlying mandibular deformity is obscured. Moreover radiography in these severely injured patients is very difficult. It is in such situations that the detection of the magnification sign is valuable in that it draws attention to fractures that may otherwise escape detection when the patient is first examined. If the fractures heal in this position the characteristic "magnification" remains even though the fractures are no longer visible (Fig. 5). Such patients may then have a clinical appearance which might suggest the presence of the "magnification sign" (Fig. 5A).

Differential diagnosis

Is there any other situation, either as a result of traumatic disturbance of the normal anatomy or of radiographic projection, which could mimic this appearance? For example, could either prognathism, on the one hand, or recession of the chin associated with mandibular neck fractures, on the other hand, produce this appearance? No, because in neither case is there actual separation of the angles of the mandible. The upper and lower teeth retain their normal relationship to each and thus no "magnification" can occur whatever the projection.

Does it make a difference if the mouth is open or shut? No. Exact comparison of the "width" of the lower jaw compared with the upper one is obviously simpler and more exact if the mouth is closed (Figs. 1, 2, 3, 4 and 5), but even if it is open anteriorly, the molars (the point of particular interest) are not far apart and the comparison between the upper and lower jaws is still valid. If there is any doubt about the presence of the sign it would obviously be prudent to obtain a film with the mouth closed to make sure that the sign is present.

Could the sign be produced by bilateral fractures of the mid-third of the face with posterior displacement of the central block, producing a fixed anterior open bite? In a large experience of maxillio-facial trauma I have never seen this. This sign is normally produced by trauma that spares the face. I have seen only one example of triple mandibular fracture and multiple facial fractures (Fig. 4). The presence of any such extensive facial trauma will at once be evident. If there is posterior displacement of the central facial block there should, in theory, be relative magnification of the *upper* jaw compared to the mandible in a postero-anterior projection. In any case there can be no lateral displacement of the ascending rami without a triple mandibular fracture however severely the face may be injured.

Does the radiographic projection ever produce spurious mandibular "magnification" as defined above? No, because the lateral distance between the corresponding molars of the upper and lower jaws is enlarged by an equal amount whether the projection is antero-posterior or postero-anterior and whatever the angle of the X-ray beam.

Associated with the two components of the magnification described above, there may be an increase in the apparent height of the horizontal ramus anteriorly produced by some displacement of the chin. It is important to realize that this alteration in the appearance of the anterior part of the mandible is *not* part of the magnification sign, even though the two findings may be associated. Variations in the position of the mandible and in the radiographic projections of it might mimic this appearance.

Thus, recognition of this important sign in a readily obtained standard radiographic projection is the signal to indicate the presence of three mandibular fractures and the need for such extra radiography as may be necessary to prove their presence.

Additional radiographic projections

If the patient is able to sit up, the simplest way of proving the presence of triple fractures is to do panoramic radiographs of the jaws, such as an orthopantomograph (Fig. 3A and B). This normally shows the fracture of the mandibular necks and the horizontal ramus all in one film. If the necessary equipment for this is not available or if the patient cannot sit up, standard lateral oblique projections showing the head and neck of the mandible will provide the same information about the mandibular necks. Sometimes the fractures here allow the mandibular heads to be displaced medially (Fig. 1) or backwards (Fig. 3B). When there is much medial displacement the mandibular head may well not be shown in the same tomographic layer of the orthopantomograph as the fracture of the horizontal ramus. Thus, when the presence of triple fractures has been detected by the "magnification sign", a special scrutiny of the condylar necks in the postero-anterior radiographs should be made to decide whether then to proceed to an orthopantomograph or to lateral oblique projections. When in doubt it is obviously prudent to use both techniques if this is possible.

An intra-oral occlusal view is the best to demonstrate the presence of a fracture in the horizontal ramus near the mid-line anteriorly. This is useful both to confirm the presence of such a fracture and to show the degree of any antero-posterior separation of the adjacent bone ends.

ACKNOWLEDGMENTS

I am deeply indebted to the radiographic staff at Queen Mary's Hospital, Roehampton, for their consistently high standard of radiography of severely injured patients. I am grateful to Mr. Ian Heslop for permission to reproduce Fig. 5(A), to the Department of Medical Photography and Illustration at Queen Mary's Hospital and Westminster Hospital for copying the radiographs and to Mrs. E. Benge for typing the manuscript.

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Book review

The Spine. A Radiological Text and Atlas. By Bernard S. Epstein, 4th edition, pp. 856. Illust. (Lea and Febiger, Philadelphia; distributed in U.K. by Henry Kimpton, London), £27·65.

It is a truism that the spine intrudes upon the practice of all branches of radiology. Since its appearance in 1955, this excellent book by Professor Epstein has become widely accepted as a standard reference work for all concerned with the radiology of the spine. It has been regularly revised at seven-year intervals and this new edition has coincided with the book's coming-of-age. The latest edition reflects the growth of knowledge of the radiological features of spinal abnormalities, having increased from 711 pages to 832. The majority of the original text is retained with pertinent new information interspersed at appropriate points. Parts have been completely re-written including, for example, a much improved account of spinal stenosis. In similar fashion the number of illustrations has been increased from 482 to 540 of which 289 are new and of uniform high quality. The arrangement of the illustrations has been improved and they are better placed in relation to the relevant text.

The book provides an inclusive account of the whole of radiology relevant to the spine. It is packed with so much carefully distilled data that continuous reading is rather heavy going. It is, however, a veritable mine of information and its use as a reference book has been greatly facilitated by the division of the previous ten sections into a total of 43 chapters, each of which is further sub-divided under the headings printed in heavy type. The references have been updated and although abundant have been suitably selected to provide easy initial directions to further reading.

There are very few shortcomings to this book. Perhaps the most obvious is the dearth of information provided about radiculography using water soluble contrast medium. It is to be regretted that the author has not used this technique to any extent because he feels that as it precludes examination of the whole spine this form of examination is contra-indicated. For this reason there is no detailed review of the indications and advantages of this technique, so widely practiced in this country. In addition, many of the original illustrations have lost something in their further reproduction and now appear rather grainy and lacking in contrast.

Despite these minor criticisms this fourth edition constitutes a new and improved version of a standard book of proven value and reputation. It should be in the library of every department of radiodiagnosis and will be regularly perused not only by radiologists but also by their clinical colleagues.

J. Roylance.

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Dimer X in hysterosalpingography

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(*Received July, 1976*)

ABSTRACT

The incidence of abdominal pain during hysterosalpingography was assessed from replies to postal questionnaires completed by 42 patients receiving Diaginol Viscous and 23 patients receiving Dimer X: the questionnaires were analysed using a double-blind technique.

In the Diaginol Viscous group, 58.5% of patients experienced moderate or severe pain during the injection as compared with an incidence of only 19% in the group receiving Dimer X. In three of the patients receiving Diaginol Viscous, there was brief loss of consciousness. Radiographic quality was satisfactory with both contrast media.

After-effects of hysterosalpingography were relatively common and included: lower abdominal pain; vaginal bleeding; temporary difficulty in walking; menstrual disturbances in subsequent periods. No correlation could be demonstrated between the type of medium used and the incidence of these after effects.

The two water-soluble contrast media commonly used for hysterosalpingography are Salpix (53% sodium acetrizoate with polivynilpyrrolidone) and Diaginol Viscous (40% sodium acetrizoate with dextran). Endografin (70% methylglucamine iodipamide) has also been recommended for this purpose. Both acetrizoate and iodipamide are considerably more toxic than currently used urographic media such as diatrizoate but, despite this, there has been little commercial impetus to produce a less toxic medium for hysterosalpingography (Ansell, 1970). In previous clinical trials (Griffiths, 1969; Sheach, 1959) comparing Salpix, Diaginol Viscous, Endografin and 76% Urografin (sodium methylglucamine diatrizoate) Diaginol Viscous appeared to have marginally fewer side effects and, until recently, this was the standard medium used for hysterosalpingography in our department. We were, however, perturbed by the relatively high incidence of abdominal pain which was occasionally associated with collapse or shock.

Bjork *et al.* (1972) investigated the use of a metrizoate dimer (Ph DZ 59 B, iozamate) for hysterosalpingo-pelvigraphy and found that it caused significantly less abdominal pain than Angiografin (65% methylglucamine diatrizoate). Dimer X (60% methylglucamine iocarmate) is a dimer of iothalamate and, like Ph DZ 59 B, it combines the advantages of reduced osmolarity and lower toxicity, so that it would be expected to be less irritant in the peritoneal cavity than the previously available hysterosalpingography contrast media. As far as we are aware, Dimer X has not previously been used for hysterosalpingography and we have, therefore, undertaken a clinical trial to assess its value for this procedure.

PATIENTS AND METHODS

Commencing in September 1974, all patients referred for hysterosalpingography received Dimer X. Patients who had undergone hysterosalpingography with Diaginol Viscous in the previous year were used as a control group.

The indications for hysterosalpingography in both groups were similar and included mainly primary or secondary infertility, or recurrent abortion.

Over the two-year period, 75 hysterosalpingograms were performed on 71 patients. Diaginol Viscous was used in 46 examinations and Dimer X in 28. Each patient in both groups was sent a questionnaire (see Appendix) some months after her hysterosalpingogram. In this, she was asked to comment on any pain or symptoms which she experienced as a result of the examination. Replies were received from 65 patients (88%): 42 out of 46 (91%) in the Diaginol Viscous group and 23 out of 28 (82%) in the Dimer X group. Three replies were invalidated. In one of these, the answers were inadequate for assessment. In the second case, the examination had been abandoned after instrumentation difficulties, whilst in the remaining case the examination had been performed under a general anaesthetic.

Hysterosalpingograms were performed by members of the gynaecological staff using either a screw tip (Leach Wilkinson) cannula or a smooth tip with olive (Everard Williams) cannula at their discretion. No sedation or pre-medication was given. A radiologist was present and controlled the fluoroscopy in all patients. In the second group of patients, when Dimer X was being used, the radiologist noted the patients' spontaneous reactions or

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complaints. Dimer X was randomly used either at room or body temperature and this was subsequently recorded, together with the volume used. In most patients, this was approximately 8 ml of the medium.

As there is now an ethical requirement for a patient to give "informed consent" in research procedures, a problem arose as to how this could be obtained without prejudicing the patient's subjective assessment of her symptoms. Although we ourselves believed that the main advantage of Dimer X was likely to be that of reduced toxicity, we were advised that it was ethically justifiable to tell the patient that the new contrast medium was being introduced "to obtain better X-ray pictures". Later in the investigation when it became apparent that there were no serious adverse reactions to Dimer X, patients were no longer informed about the contrast medium.

RESULTS

As the questionnaires were returned, they were checked by one of us (G.A.) to monitor the progress of the investigation and to ensure that there were no unforeseen complications from the use of the new medium.

At the conclusion of the investigation, the questionnaires were numbered in a random fashion and the patients' names and dates of examinations were occluded so that it was not possible to recognize which contrast medium had been used in each case. They were then presented to one of us (G.C.M.) for assessment.

Immediate side effects

On the basis of each patient's reply, the pain experienced during and immediately after injection of contrast medium was initially rated on a four-point scale as follows: no pain, Grade 1; slight pain, Grade 2; moderate pain, Grade 3; severe pain, Grade 4.

TABLE I

SCORING SYSTEM CORRECTED FOR INSTRUMENTATION AND PAIN THRESHOLD

Pain on instrumentation	Pain during injection			
	None	Slight	Moderate	Severe
None	1	2	3	4
Slight	0.5	1.5	2.5	3.5
Severe	0	1	2	3

Since, however, the patients were also subjected to instrumentation, this could have complicated the attribution of the pain to the subsequent contrast medium injection. We therefore attempted to correct for this by an assessment of "pain experienced during instrumentation" which was then subtracted from the contrast medium score. Judging from the answers to the questionnaires, the great majority of patients were, in fact, able to distinguish fairly accurately between the two parts of the investigation. The degree of correction made for pain during instrumentation was arbitrarily rated as follows: slight pain—0.5; moderate to severe pain—1. In this way, we also hoped to introduce a correction factor for individual variations in pain threshold, since a patient with a low pain threshold would be more likely to complain of symptoms during instumentation and *vice versa*. Thus, for example, the corrected score for a patient who had severe pain during instrumentation and none during injection would be "0" whilst the score for a patient who had no pain during instrumentation and severe pain during injection would be "4". The range of corrected scores is shown in Table I.

The average score for patients receiving Dimer X was 1.3 as compared with an average score of 2 in patients receiving Diaginol Viscous. This difference is statistically significant ($P < 0.02$). The histogram in Fig. 1 shows the distribution of pain scores in the two groups of patients and it becomes evident that the majority of patients receiving Dimer X have low pain scores whereas the higher pain scores were predominantly in the Diaginol Viscous group. This becomes more obvious if one compares the incidence of minor symptoms (Grades 0–1.5) with that of moderate and severe symptoms (Grades 2–4) shown

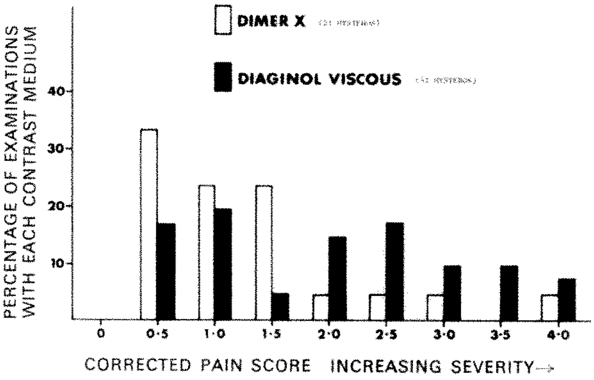

FIG. 1.
Distribution of corrected pain scores.

TABLE II

SEVERITY OF PAIN DURING HYSTEROSALPINGOGRAPHY

Contrast medium	Minimal pain (Grades 0–1.5)	Moderate to severe pain (Grades 2–4)
Dimer X (21 hysteros)	17 (81%)	4 (19%)
Diaginol Viscous (41 hysteros)	17 (41.5%)	24 (58.5%)

in Table II. Thus, in the Dimer X group 81% had only minor symptoms and 19% had moderate or severe symptoms. By contrast, the trend in the Diaginol Viscous group was reversed, with 58.5% of patients experiencing moderate or severe pain and only 41.5% being classified as minor. There did not appear to be any correlation between the temperature of the injected Dimer X and the incidence of pain.

After effects

Of the 62 valid questionnaires, two were incomplete in the "after effects" section. The total series in this section was thus 60. Only 13 patients of the 60 were completely symptom free immediately after leaving the X-ray table. The commonest after effect was low abdominal pain (often described as "period pain"); this occurred in 26 patients (43%). In the majority of these patients the pain lasted up to 24 hours but three patients experienced discomfort for a week.

Vaginal bleeding occurred in 18 patients (30%) and was sometimes associated with abdominal pain. Blood loss ceased within 24 hours in nine patients, in three of the remainder it lasted up to a week. Menstrual disturbances occurred in seven patients during subsequent periods. Three patients in the Diaginol group briefly lost consciousness a short time after the examination. Ten patients from both groups stated they felt faint: this was often associated with other symptoms. Seven patients complained of difficulty in walking, and even on standing or sitting erect. This symptom was of short duration, usually a few hours. Less common ill effects were perineal discomfort in five patients, dyspareunia in one and backache in three.

Apart from the three cases of loss of consciousness, there was no significant difference in the incidence of after-effects between the two contrast media.

Radiographic quality

The radiographs of the hysterosalpingograms were also assessed by G.C.M. using a "double-blind" technique. No difference in the opacity of the contrast media could be detected in the two groups of patients and the radiographs were equally satisfactory for diagnostic purposes.

DISCUSSION

Water-soluble contrast media have many advantages in hysterosalpingography but a major disadvantage has been their tendency to cause pain on injection which may, occasionally, be severe. In this preliminary investigation, we have shown that Dimer X causes significantly less pain when used for hysterosalpingography than Diaginol Viscous. This effect is probably partly due to the reduced chemical toxicity of the iocarmate molecule in comparison with acetrizoate, and in part to its lower osmolarity per unit of iodine. The localized chemotoxic effect on the tissues is distinct from the rarer generalized hypersensitivity reactions which may occur with contrast media. One of our patients receiving Diaginol Viscous, who was not included in the present survey, experienced a severe hypersensitivity reaction without any preceding abdominal pain. The reaction commenced with a numb feeling in her face after which she became flushed. Fifteen minutes later, she recovered temporarily then vomited, became pale and was severely hypotensive. Her condition improved gradually over the next half hour. This reaction could have been due either to the acetrizoate or to the dextran thickening agent used in the Diaginol Viscous, since dextran itself can cause a similar type of reaction to that of iodine contrast media. Although Dimer X has been available for at least five years, the indications for its use have been restricted and it is not yet possible to get a reliable assessment of the incidence of possible hypersensitivity reactions.

It has usually been considered desirable for hysterosalpingography media to have a relatively high viscosity. Diaginol Viscous has a viscosity of 100 centipoises at 37°C. Dimer X is more fluid, its corresponding viscosity being only 7.2 centipoises. This fluidity, however, did not create any technical problems: the uterus and tubes filled rapidly. Indeed, it was our impression that cornual spasm was less frequent with Dimer X than with other water soluble media but we have no objective proof of this. The iodine content of Dimer X (280 mg/ml) is similar to that of Diaginol Viscous (263 mg/ml) and the radiographic quality was satisfactory.

The main disadvantage of Dimer X is its cost. At current hospital prices, 10 ml of Dimer X costs £6·70 in comparison with a cost of £1·14 for 10 ml of Diaginol Viscous. However, we feel that the added welfare to the patient of using a less painful material for this intimate and emotionally stressful type of investigation justifies the increased cost, even in the present conditions of financial stringency. On the evidence which we have at present, we would be unwilling to return to the use of the more toxic media for hysterosalpingography.

In this particular series it was impossible to separate the aetiology of the individual side effects. For instance, bleeding and fainting are expected sequelae of cervical dilatation, whereas "period pains" could be equally attributable to either uterine distention, cervical dilatation or peritoneal irritation. Menstrual disturbances which occurred in many of the patients are similarly of uncertain aetiology. The incidence of perineal discomfort was surprisingly low.

An unusual and, to the best of our knowledge, previously unreported after effect was that of difficulty in walking, sitting or standing. This symptom was always of short duration, usually six to eight hours. It occurred with both contrast media and in one case the pain became so severe that the patient was "nearly crawling" when she reached home. None of our patients was put up in lithotomy stirrups. In some of these cases, pain was first noticed when the patient sat in the erect position. This suggests that there may have been referred pain due to peritoneal irritation from the contrast medium. Another possibility is that the discomfort on walking may have been due to the use of the vaginal speculum. If this were so, one would have expected a higher incidence of perineal discomfort. Nevertheless, it would be interesting to conduct a similar type of survey amongst out-patients having other gynaecological examinations.

SUMMARY

Dimer X caused significantly less severe pain during hysterosalpingography than Diaginol Viscous, but there was no appreciable difference in the incidence of late side effects. Radiographic quality was satisfactory with both contrast media.

ACKNOWLEDGMENTS

We are grateful to Messrs May & Baker Ltd., for a generous supply of Dimer X. We should particularly like to thank Mrs. S. Hughes who was responsible for the secretarial work involved in the investigation and we should also like to thank the radiographic and nursing staff of our department for their help. Finally, we should like to pay tribute to the patients whose co-operation in responding to the questionnaires made this study possible.

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APPENDIX

Patients were asked to answer the following questions in a postal questionnaire.

1. Did you have any discomfort or other symptoms while the instrument was being placed in the womb but *before* the radiologist watched the injection on the television screen? If so, please describe the symptoms etc.	Yes* No*
2. Did you have any discomfort or other symptoms *after* the radiologist started to watch the injection on the television screen? If so, please described the symptoms etc., stating how soon after the start of the injection they occurred and how long they lasted.	Yes* No*
3. Did you have any discomfort or other symptoms after you left the X-ray table or during the next 12 hours? If so, please give details including time of onset, and how long the symptoms lasted.	Yes* No*
4. Did you have any discomfort or other symptoms on the day after the examination, or at any time in the two weeks that followed? If so, please describe the symptoms stating when they occurred and how long they lasted.	Yes* No*

Copies of the explanatory letter and questionnaire are available on request from G.A.

1977, *British Journal of Radiology*, *50*, 105–109

The less familiar manifestations of schistosomiasis of the urinary tract

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ABSTRACT

One hundred and fifteen patients with schistosomiasis of the urinary tract were studied. Sixty-five per cent of the ureters showed striking deformities, including medial deviation, a straight lumbar course, and in the pelvic segment a bowed appearance with medial and cranial displacement at the vesiço-ureteric junction. This appearance, which resembles a "cowhorn", is due to fibrosis in the bladder trigone.

Stasis and dilatation of the upper urinary tract were present in the absence of mechanical obstruction. Strictures were rare (7%), and fluoroscopy during excretory urography confirmed that the changes in the upper urinary tract were due to functional derangement of the ureters and not strictures. Four patterns of bladder calcification are described—the familiar linear rim calcification, an amorphous form, uniform opacity and curvilinear forms.

The diagnosis can be suggested from the post-micturition bladder film which shows a coarse, shaggy or polypoid mucosal pattern in all stages of the disease.

PATIENTS AND METHODS

One hundred and fifteen patients with confirmed infestation by *S. haematobium* were studied. Thirty eight were studied retrospectively from the urology clinic and 77 were referred to the X-ray department from both medical and surgical departments.

There were 66 males and 49 females; their ages ranged from nine to over 70 years. All had excretory urography with at least 40 ml sodium iothalamate 70% (Conray 420). In 49 patients ureteric movement was studied fluoroscopically. Increased peristalsis was defined as over 12 waves per minute and decreased peristalsis as less than four waves per minute. Eleven patients underwent retrograde pyelography and ten were examined by micturating cystography.

FINDINGS

Calcification in the urinary tract

This was found in 72 patients. In 42 it was confined to the bladder, in ten to the ureters, and in 22 patients both bladder and ureter(s) were involved. Eight patients had opaque stones of various types in the urinary tract, including one in the posterior urethra (Fig. 1).

Ureteric calcification was more common on the left side (11 to 5); the calcification was usually "tram line" in appearance and was confined to the lower third of the ureters. In one case, however, the entire ureters were involved.

Four patterns of bladder calcification were recognized; 63% had the familiar linear rim calcification; 18% had wavy linear calcifications (Fig. 2) simulating a post-micturition film; 12% had a "cumulus cloud" appearance (Fig. 3), and 6% presented as homogeneous opacity in the bladder (Fig. 4).

UPPER URINARY TRACT

Dilatation. This was seen in 46 patients (40%). In 34 kidneys, there was pyelocaliectasis—30 of these also showed segmental or generalized ureteric dilatation. A further 23 showed segmental or generalized dilatation without pelvicaliceal change. Kinks and crisp extrinsic impressions (*e.g.* due to psoas and vessels) were common in dilated ureters.

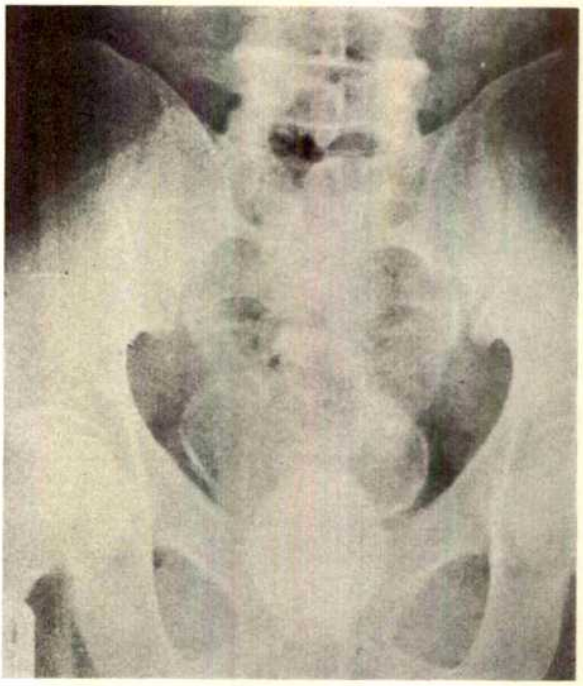

FIG. 1.

Bladder calcification and associated large calculus in the prostatic urethra.

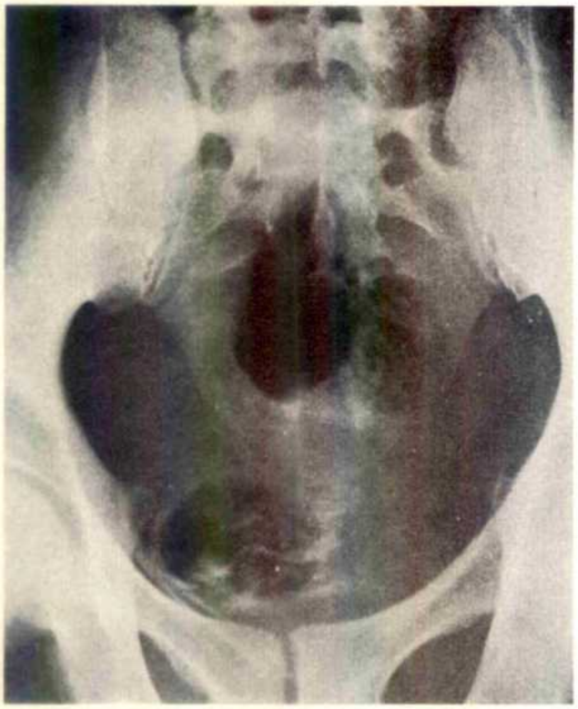

FIG. 2.

Wavy calcified lines in the bladder simulating a post-micturition film of an excretory urogram. This pattern is due to bladder emptying: in a full bladder the calcification will assume the familiar rim form.

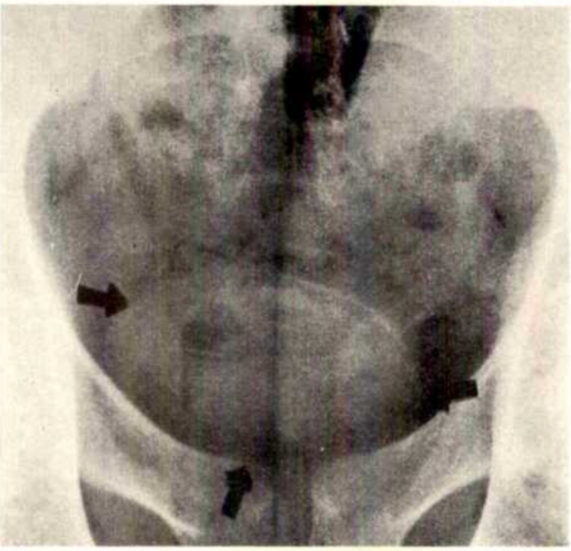

FIG. 4.

Faint homogeneous calcification in the bladder.

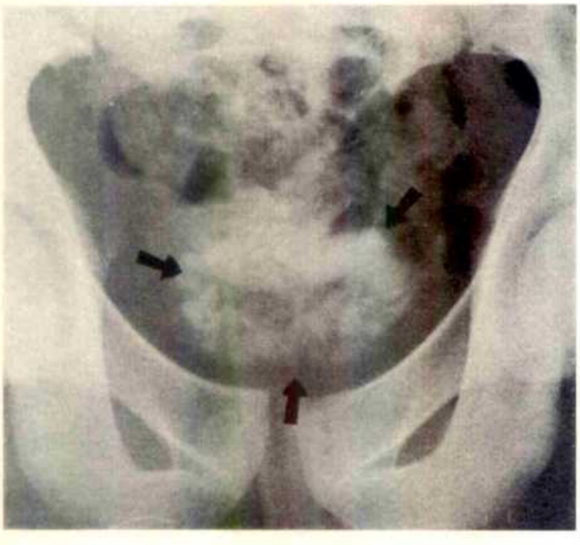

FIG. 3.

Bladder calcification in this case is amorphous.

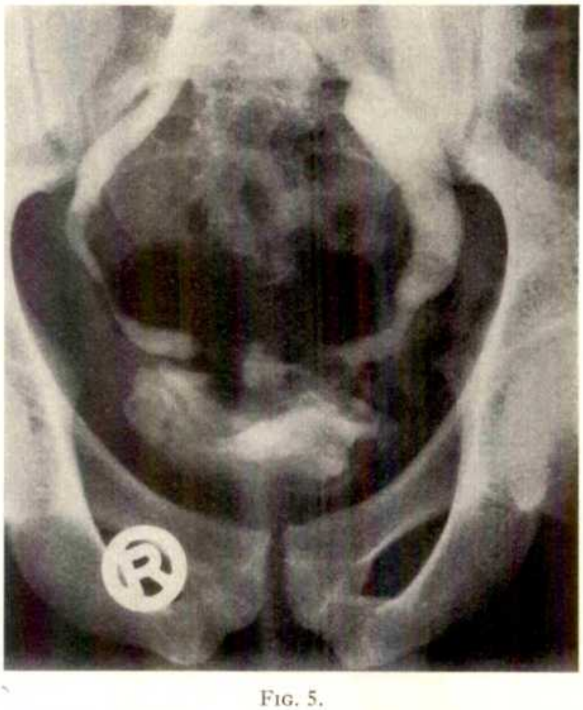

FIG. 5.

The lower ureters show a characteristic bowed appearance with medial and cranial displacement of the terminal ends, due to trigonal fibrosis—("cowhorn deformity"—see Figs. 6 and 7). Note also the abnormal folds of the bladder.

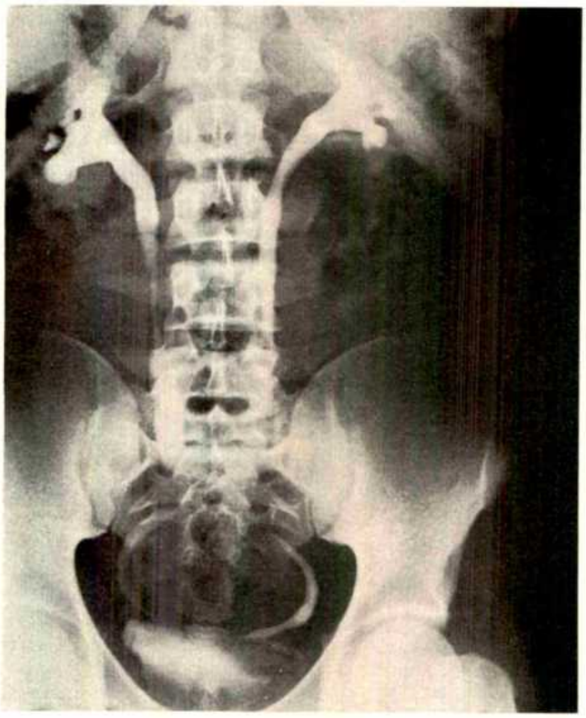

FIG. 6.

In the lumbar segments, the ureters are straight and medial. The characteristic deformity described in Fig. 5 is again shown in the distal thirds of the ureters. The appearances of this urogram were static for about 40 minutes after release of compression.

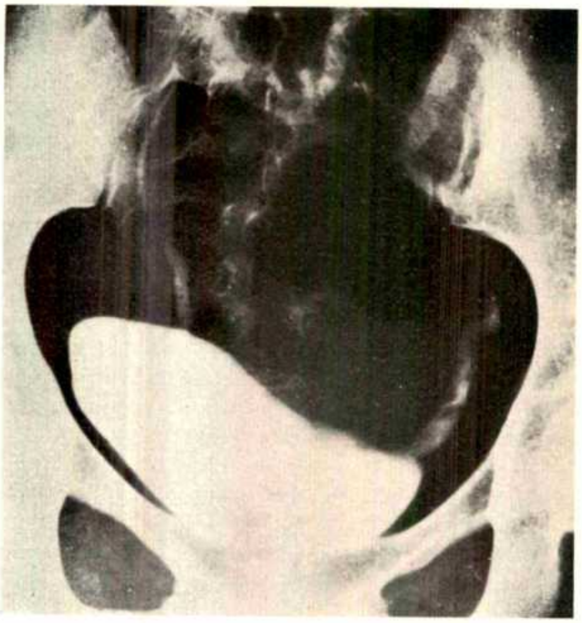

FIG. 7.

Filling defects in the lower left ureter due to granulomata.

Deformity of the ureters. A characteristic deformity of the ureters resulted in a medial and straight course of the lumbar ureter. In the terminal segment there was medial as well as cranial displacement due to trigonal fibrosis in the bladder. This gives an appearance likened to a "cow horn" and was present in 61% of the cases (Figs. 5, 6 and 7).

Ureteric stasis. In 21 patients there was marked ureteric stasis so that the outlines of the ureters did not alter in serial films taken after release of compression (Fig. 6).

Other less common findings. (i) Polypoid ureteric defects in 39 ureters (Fig. 7); (ii) strictures—pelvi ureteric two, mid-ureter three, pelvic two, vesicoureteric nine; (iii) cobra head deformity in lower ends of two ureters (Fig. 8) was found in two cases.

Loss of movement of the ureters

Fluoroscopy was performed in 23 urographically normal patients and 26 with ureterectasis. In the "normal" group, 12 showed increased peristalsis, 15 ureters (28%) showed normal upper ureteric movement and 15 had hypotonic ureters. The remainder had varying degrees of reduced motility. In

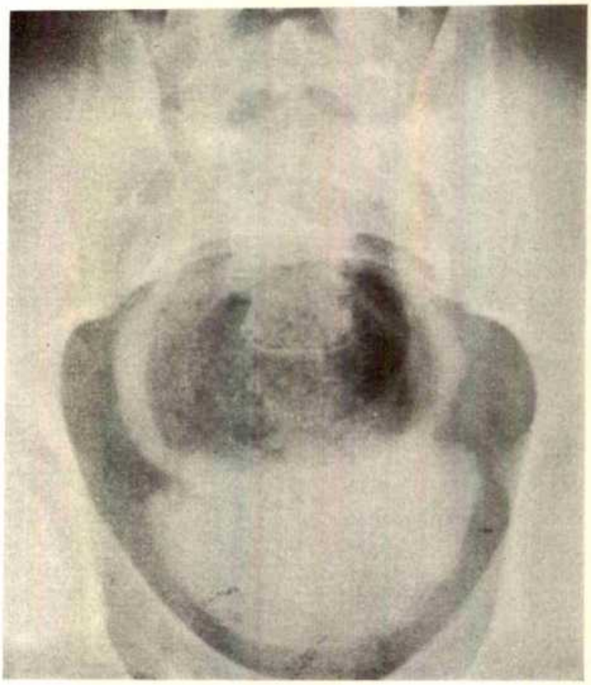

FIG. 8.

In addition to the characteristic deformity of the lower ureters, there is "cobra head" dilatation of the terminal right ureter.

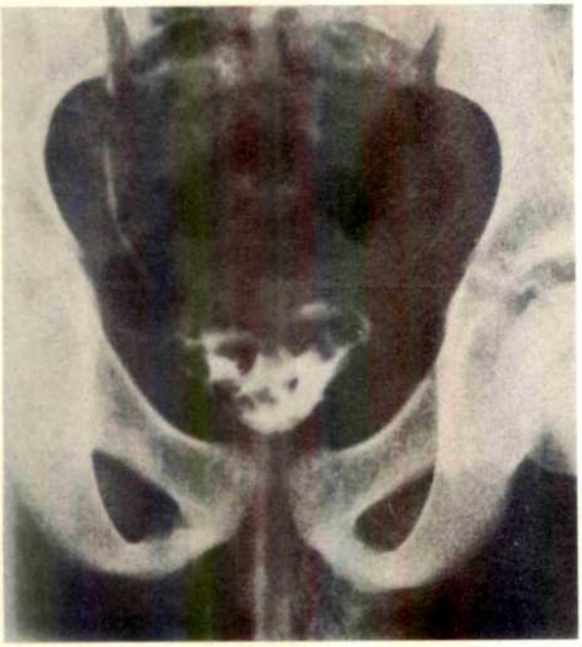

FIG. 9.

Post-micturition film shows very coarse polypoid defects in the bladder of a nine-year-old patient. Many of these defects resolved with treatment.

TABLE I

ABNORMALITIES FOUND IN THE BLADDER

Total number of bladders	115
Abnormal mucosa	99 (86%)
Calcification	64 (56%)
Associated calculi	5 (4%)
Carcinoma	2 (2%)

TABLE II

ABNORMALITIES IN THE UPPER URINARY TRACT

Total number of patients (nephrectomies in 2 patients)	115
Total number of kidneys	228
Pyelocaliectasis	34 (15%)
Generalized ureteric dilatation	40 (17%)
Segmental ureteric dilatation	13 (11%)
Strictures	16 (7%)
DEFORMITIES	
1. (a) Medial deviation in abdomen only	18
(b) Characteristic deformity in distal thirds	68 } 148 (65%)
(c) Combination of (a) and (b)	62
2. Gross tortuosity	41 (18%)
Polypoid defects in ureters	39 (17%)
Calcification in ureters	32 (14%)

the lower segments only two ureters showed normal movement; 18 were hypotonic while the rest were aperistaltic. In all these cases drainage was improved in the upright or prone position.

Bladder appearances

The various types of calcification occurring in the bladder have been mentioned. For reasons discussed below, all the stages of bladder disease may give rise to coarse bladder mucosal folds and polypoid defects (Fig. 9). Vesical diverticula were present in three cases and carcinoma in two.

PATHOLOGY

In both ureter and bladder the pathological process may be divided into acute and chronic stages. The disease usually starts in the trigone and base of the bladder with submucosal pseudo-tubercles or granulomata and hyperplastic epithelium which in severe cases show pseudo-papillary hyperplasia. The acute stage has been variously described but it is generally likened to sago grains. Although the sandy patch synonymous with the chronic disease denotes atrophic mucosa, epithelial cell disorder may result in cystitis glandularis and cystitis cystica, reflected in polypoid defects in the bladder film. Moreover the chronic disease is frequently complicated by infection giving rise to thickened mucosal folds. Coarse bladder mucosal folds with or without defects are thus common to all three stages of the disease. At the acute stage the ureters usually show moderate dilatation with or without defects (granulomata). The chronic disease supervenes with early fibrosis, gross dilatation and tortuosity.

DISCUSSION

In this series, there was a low prevalence of true strictures (7%). This is at variance with the pathogenesis suggested by some authors, who describe dense fibrosis involving the whole of the ureteric wall and causing stenosis with dilatation above it (Badenoch, 1974). In fact, other workers have also shown that strictures are infrequent, for example 4% vesico-ureteric strictures seen at cystoscopy by Dubey (personal communication) and 3.1% in Gelfand's series (1950).

Although there is some variation in the nature and severity of lesions in different geographical locations, it is likely that the hypotonic and atonic condition of chronically diseased ureters is the cause of most ureteric dilatation. There are two possible reasons why strictures may be erroneously diagnosed—one is the "cow horn deformity" of the lower ureters caused by trigonal fibrosis which makes catheterization of the ureters very difficult; the other is the presence of polypoid lesions due to granulomata at the vesico-ureteric junction.

The well known complications of carcinoma of the bladder and calculi are confirmed in this study. Calculi which are ordinarily rare in this population were present in 8% of the cases. However, the grossly contracted bladder seen in Egypt (Hashem 1961) and Rhodesia (Honey and Gelfand, 1960) was not found in this series.

ACKNOWLEDGMENTS

Grateful thanks to the Medical Illustration Department of the University of Zambia for the photographs of the radiographs and to Miss C. Thornicroft for typing the manuscripts.

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Book review

Radioisotopes in radiodiagnosis. By A. S. Bligh, E. R. Davies and K. G. Leach, pp. x+230, 1976 (Butterworths, London), £10·00.

This neat little book, written by a neuroradiologist, a general radiologist and a physicist, sets out with the intention of providing an introduction to radioisotope imaging for candidates for the D.M.R. and F.R.C.R. examinations. Between them the authors have a good deal of personal experience both of radioisotope imaging and of teaching candidates for these examinations, and their joint experience has been put to good use. It is well written and well produced, with concise, clear chapters and restricted but pertinent illustrations.

Inevitably, some chapters will have been overtaken by events before a book is published, and this has indeed happened in the case of Chapter 13, on the cardiovascular system, which is already obsolete.

It is reasonable in a book at this level not to include detailed references, although one feels that some suggestions for further reading might be useful. The only references found in the book are a number in Chapter 8 and one in Chapter 9 which are cited in the text but not listed anywhere, so that it would be impossible to follow them up. Two other proof reading errors were noted, on page 121 in the caption to Fig. 8.1 "infection" is printed for "injection" and on page 208 where "57Cr" is printed for "57Co".

There are a number of places where, in their attempt to keep the text brief and simple, the authors may be criticized for over-simplification. Thus, in their discussion of the accuracy of brain scanning, they do not bring out the point that the patients selected will greatly affect the incidence of false positive and false negative results. Patients referred to a neurosurgical centre will, in general, have a higher incidence of tumours and these will tend to be larger. False negatives are therefore much less commonly seen in radioisotope units serving neurosurgical units. In other units where there is a much less highly selected group of patients being referred, many of whom will have either no tumours or very small tumours, the incidence of false negative examinations will inevitably be much higher. On page 141, in the discussion on agents for examining the kidneys, technetium DTPA is included with the weaker chelates such as gluconate and glucohephtonate. This is wrong and misleading as the two groups behave quite differently *in vivo* and are useful for different purposes. In the discussion on isotope cysternography, no mention is made of indium 111 DTPA which is generally considered to be the best available agent.

However, the principle criticism of this book is that the authors have set their sights too low. They have undoubtedly achieved their ambition of providing a sound introduction to the physical and clinical background to the commoner imaging techniques with which they themselves are most familiar. However, it is clear that the future of nuclear medicine lies more in dynamic investigations of function and less in static imaging, as alternative techniques of imaging such as ultrasound and CT scanning are becoming more developed and more generally available. Although some mention is made of dynamic studies of the brain and of renography, there is really too little to give any enthusiasm to the student or to make clear the potential value of these and other dynamic techniques.

Undoubtedly this book succeeds in achieving its declared objectives, namely to give an introduction to radioisotope imaging to postgraduate trainees principally in radiology but also in other specialties. However, I feel that its objectives are too narrow and limited and that it gives too restricted a view of the role that nuclear medicine now holds. For this reason I would not recommend it to my own students.

M. V. MERRICK.

1977, *British Journal of Radiology*, *50*, 110–112

Fetal complications of amniography

By P. Grech, M.D., F.R.C.R., D.M.R.D.,* and L. Spitz, F.R.C.S.†

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(*Received August, 1976*)

ABSTRACT

In a series of 241 amniograms, there were two cases of fetal tissue damage resulting from the subcutaneous injection of contrast material. Details of these two cases are given and the damage sustained illustrated. Measures designed to prevent such complications are outlined, together with recommendations for its management, should such a complication occur.

Several recent reviews have stressed the relative safety and low incidence of complications associated with amniography (McClain, 1964; Lennon, 1967; Queenan *et al.*, 1968; Spindola-Franco *et al.*, 1969; Grech, 1975). During the past eight years (1968–1975) 241 amniograms were performed in Sheffield. No maternal complications were recorded but in two cases fetal tissue damage was caused by the subcutaneous injection of radio-opaque contrast material.

The purpose of this paper is to highlight the potential fetal hazards of amniography and to recommend measures designed to prevent such complications.

CASE REPORTS

Case 1

B scan performed on a 29-year-old female (para 3 gravida 7) at 35 weeks' gestation revealed a posterior placenta extending towards the fundus of the uterus and a breech presentation. The biparietal fetal skull diameter measured 9.8 cm. The fetal trunk diameter was 7.4 cm, significantly smaller than the size expected in relation to the measured skull diameter and giving the clinical impression of hydrocephalus. These findings were confirmed at a repeat scan performed one week later.

Because of the poor obstetrical history coupled with the reluctance to perform an elective caesarean section in the possible presence of a grossly hydrocephalic infant, feto-amniography was carried out at 36 weeks of gestation. Analysis of the liquor amnii revealed an α fetoprotein level of 4 pg/ml amniotic fluid (slightly elevated).

The feto-amniogram was performed by injecting 32 ml of Conray 280 and 5 ml of myodil into the amniotic sac. During the injection of these agents the fetus suddenly moved. Thereafter resistance to the flow of contrast was noted. The injection was discontinued and the needle repositioned before the remainder of the contrast was run in. The amniogram showed a well formed normally proportioned fetus. The fetal bowel was outlined but detail obscured by an opacification in the anterior abdominal wall of the fetus (Fig. 2A). Three days later a 2300 g female infant was delivered by low segment caesarean section. A 4 × 2.5 cm area of necrosis surrounded by a 2 cm circumferential rim of erythema was present in the right flank (Fig. 1). A radiograph revealed a densely opacified area in the region of the necrotic abdominal wall (Fig. 2B).

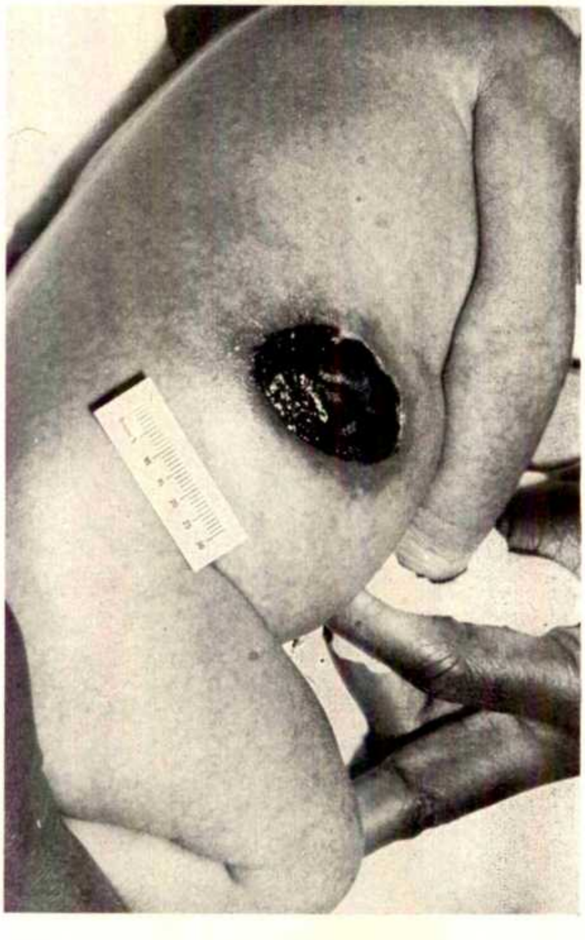

FIG. 1.

Showing necrotic area in right flank in Case 1. Note the surrounding inflammatory reaction.

No active surgical procedures were adopted and the necrotic tissue gradually separated from the underlying tissue leaving a healthy granulating surface which slowly epithelialized from the edges. The lesion was completely healed within five weeks, leaving minimal scarring and deformity.

Case 2

A 34-year-old female was referred for Rh-isoimmunization. She had a normal delivery nine years previously but the subsequent pregnancies four and five years later both resul-

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*Consultant Radiologist.

†Consultant Paediatric Surgeon, and reprint requests.

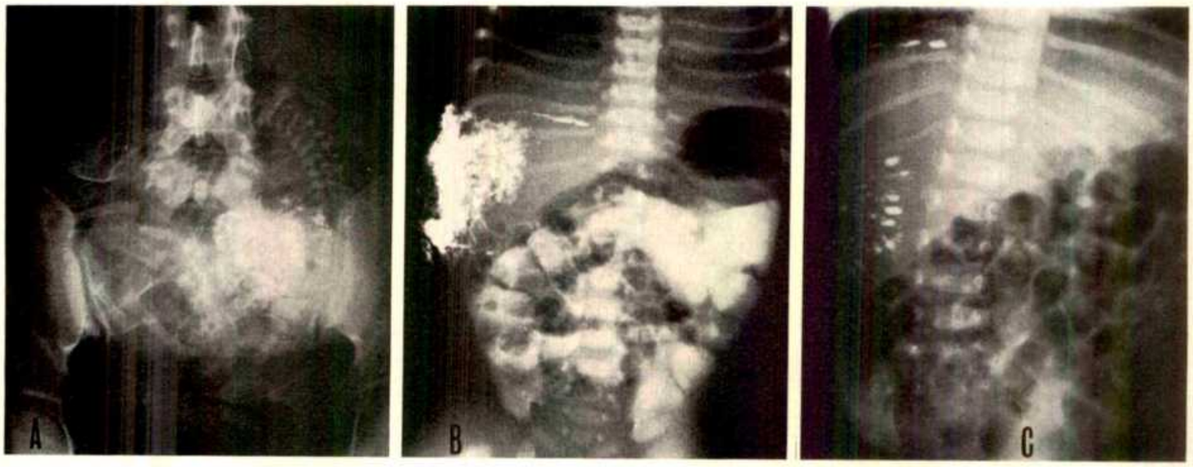

FIG. 2.

Feto-amniography in Case 1.

(A) Radiograph taken six hours after the injection of contrast media shows some opacification of the fetal small bowel, but the bowel outline is obscured and detail is poor on account of a diffuse shadow which was thought to be contrast in the soft tissue of the baby. It was also noted that the fetal skin is not well outlined by the myodil.

(B) Radiograph of the baby after birth confirming the good opacification of the fetal bowel and contrast agent in the right flank. Note the linear shadow along the upper border of the liver.

(C) Radiograph of the baby's abdomen at the age of four weeks. Most of the contrast in the soft tissue has been absorbed but there are still some globules of contrast. The higher density, and the delayed disappearance suggest that this must have been the myodil part which was injected in the soft tissue.

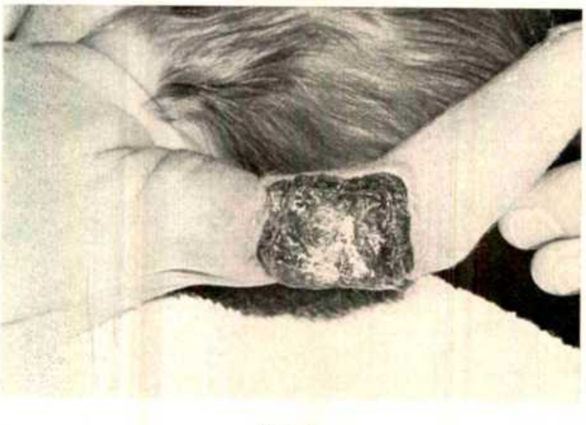

FIG. 3.

Area of necrosis on the posterior aspect of arm in Case 2.

ted in stillbirths. A ^{99}Tc placentogram showed the placenta to be in the left cornual position. This was followed by an amniogram employing 35 ml of Conray 280 which showed a 33-week fetus in a breech presentation and of normal appearance. The fetal intestines were well outlined showing a good "vitality test". An intrauterine transfusion was carried out the following day. Three days later a 34-week gestational age normal female infant weighing 1900 g was delivered. Two post-natal exchange transfusions were required in order to control the hyperbilirubinaemia. At birth a 3 × 3 cm area of necrosis was noted in the posterior aspect of the right upper arm (Fig.3). Spontaneous separation of the necrotic tissue was allowed to take place, following which healing by epithelialization and cicatrization occurred.

DISCUSSION

The indications for invasive investigative procedures of the pregnant uterus are restricted by potential maternal and fetal complications. In order to limit inappropriate fetal injection of contrast material it is essential to ascertain the correct position of the amniography needle as implied by unimpeded backflow of liquor amnii on aspiration prior to injection of any contrast medium. Sudden movement of the fetus during the injection or any unexpected increase in resistance to the flow of contrast is an absolute indication to stop the infusion forthwith and to ascertain that the needle is properly positioned before completing the injection.

The definitive treatment, should skin necrosis supervene, is initially conservative. Secondary contamination should be avoided by frequent application of an antiseptic solution (*e.g.* 1% solution of mercurochrome). Separation of the necrotic tissue from the underlying granulating surface takes place spontaneously and epithelialization occurs from the periphery of the lesion with minimal cicatrization.

Attempts at primary excision and skin graft or secondary suture are unnecessary.

The dramatic effect of subcutaneous injection of radio-opaque contrast material, whether a fat soluble (as in Case 1) or water soluble (as in Case 2) in the human fetus is surprising in view of the relatively inocuous effect in man.

Notes: Conray 280: Meglumine iothalamate 60% w/r containing 280 mg iodine in combined form per ml (May & Baker).

Myodil: Iophendylate injection containing 30% of organically combined iodine.

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Book review

Radiology of renal failure. By H. J. Griffiths, pp. 296, Illust., 1976 (W. B. Saunders Co.), £14·75.

It was a great pleasure to read this new addition to the ranks of radiological textbooks which has appeared at a particularly opportune time. With the wider application and improving success of renal dialysis and transplantation, there are increasing numbers of patients with chronic renal failure in the community. As these patients are no longer confined to a few specialist units they may present for radiological assessment to any district general hospital. This succinct account and a clear explanation of the radiological intricacies of renal failure will be welcomed by all.

The book is a slim volume of nearly 300 pages with abundant high quality illustrations. There is an excellent synopsis of the pathophysiology of uraemia by a guest writer, Professor G. M. L. Bailey. The chapters on renal osteodystrophy and renal transplantation provide excellent reviews of current world opinions which have been correlated with the impressive personal experience of the author. The chapter on the diagnosis of renal failure and the use of intravenous pyelography is a little disappointing and exemplifies the difficulties in selection between those topics relevant to this book from those best left to the general textbook of uroradiology. The accounts, for example, of the radiological diagnosis of causative diseases are too brief to be helpful and would have been better omitted. There is an excellent chapter devoted to special procedures dealing with bone mineral analysis, xeroradiography, and reviews of ultrasound, angiography and radionuclides by guest authors. While these contributions are of a very high standard many readers will regret that the relevant parts are not incorporated in the definitive accounts elsewhere in the book. There is a first class well selected bibliography of over 450 references including a good review of the British literature.

The book has succeeded in providing a sound foundation for the study of problems of renal failure, with clear directions for further reading of original articles. Above all, the clarity of style and logical order of presentation encourages the reader to finish the whole book before setting it aside. It will be an invaluable addition to radiodiagnostic departmental libraries.

J. ROYLANCE.

1977, *British Journal of Radiology*, *50*, 113–115

Urethral stone formation following urethroplasty

By **R. J. Godwin, M.A., M.B., B.Chir., M.R.C.P. (U.K.), D.M.R.D.**

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(*Received August, 1976*)

ABSTRACT

Two patients formed urethral stones on hair growing within the urethra following urethroplasty, an uncommon complication of this operation. The technique of urethrography is important. A control exposure is essential at the start of any examination, and a post-micturition film can aid in better demonstration of stones.

Debenham in 1930 first emphasized the importance of local abnormality in the urethra, as a predisposing cause for either the development of a primary stone, or impaction of a migrating stone. Two cases are described below which exhibit an unusual cause of urethral stone formation.

CASE HISTORIES

Case 1 Aged 39

In 1951 he sustained a ruptured urethra in an accident. An end-to-end anastomosis was performed, resulting in a stricture formation. This was treated with intermittent dilatation from 1951 to 1969, when a two-stage urethroplasty was performed.

In 1975 he presented again with a history of a poor stream, occasional dysuria and terminal dribbling, following bruising to his perineum in a further accident.

On examination the external appearance of the urethra was satisfactory and no stones were felt.

Case 2 Aged 25

At birth he was found to have hypospadias and bilateral undescended testes. At age 7, 12 and 13 years operations were performed to enable urethroplasty and orchidopexy.

At the time of presentation in 1976 his complaints were of persistent dribbling of urine with a poor stream, and also intermittent leakage of urine at the base of the penis.

On examination the urethral meatus was on the underside of the penile shaft. No meatal stenosis was present and no stones were palpable. An area of induration at the base of the penis was seen, but no definite fistula found.

INVESTIGATION

In both cases ascending urethrography was performed as better distension of the urethra is possible with this method.

No attempt was made to empty the bladder prior to the examination. A Knutson's clamp was used in Case 1, whilst in the second case, contrast medium was injected using a small Foley catheter (de Lacey *et al.*, 1973).

Following exposure of a control film, "Umbradil" was injected under screening control, and films taken in the 45 deg. supine oblique position. Following this, the patient was asked to micturate. A final oblique film was taken to include the urethra and bladder.

In both cases the control films demonstrated opacities in the region of the urethra, previously unsuspected clinically (Fig. 1A, B).

The films of the contrast-filled urethra confirmed that the opacities lay within the urethra, and demonstrated in Case 2, the rather tortuous course of the penile urethra. The stones were apparently immobile, and no associated strictures or diverticula could be demonstrated. Following micturition the stones were well shown, coated with the viscous contrast medium (Fig. 2A and B).

In neither case was a urethral calculus suspected prior to urethrography, although palpable on reexamination.

OPERATIVE FINDINGS

At operation in Case 1, two urethral stones were found. The more distal stone was removed at urethroscopy, and the larger, more proximal bulbar stone by urethrotomy. Both stones contained embedded hairs, and the larger stone was attached by hairs to the region of the urethroplasty (Fig. 3).

In Case 2, a stone in the urethra was found containing embedded hair and also attached to the urethroplasty by hairs. A second, smaller stone was found in a fistulous track to the base of the penis. Both stones were removed and the fistula excised.

DISCUSSION

Some urethral calculi formed in the upper urinary tract are arrested during passage through the urethra, others are formed in the urethra. An associated urethral abnormality is often, although not necessarily, present. This is commonly a stricture or diverticulum (Debenham, 1930; Amin, 1973).

With the increased incidence of major pelvic trauma, urethral injuries have an increased incidence and present a challenge, both in diagnosis and treatment (Gibson, 1974; de Lacey *et al.*, 1973). Some post-traumatic strictures can be adequately managed by intermittent dilatation, but others, for more permanent relief of symptoms, may need a urethroplasty (Turner-Warwick, 1960; Devine *et al.*, 1968; Blandy and Singh, 1975; Orandi, 1968).

The methods of urethroplasty are many, but the majority entail the use of a skin inlay, either as a

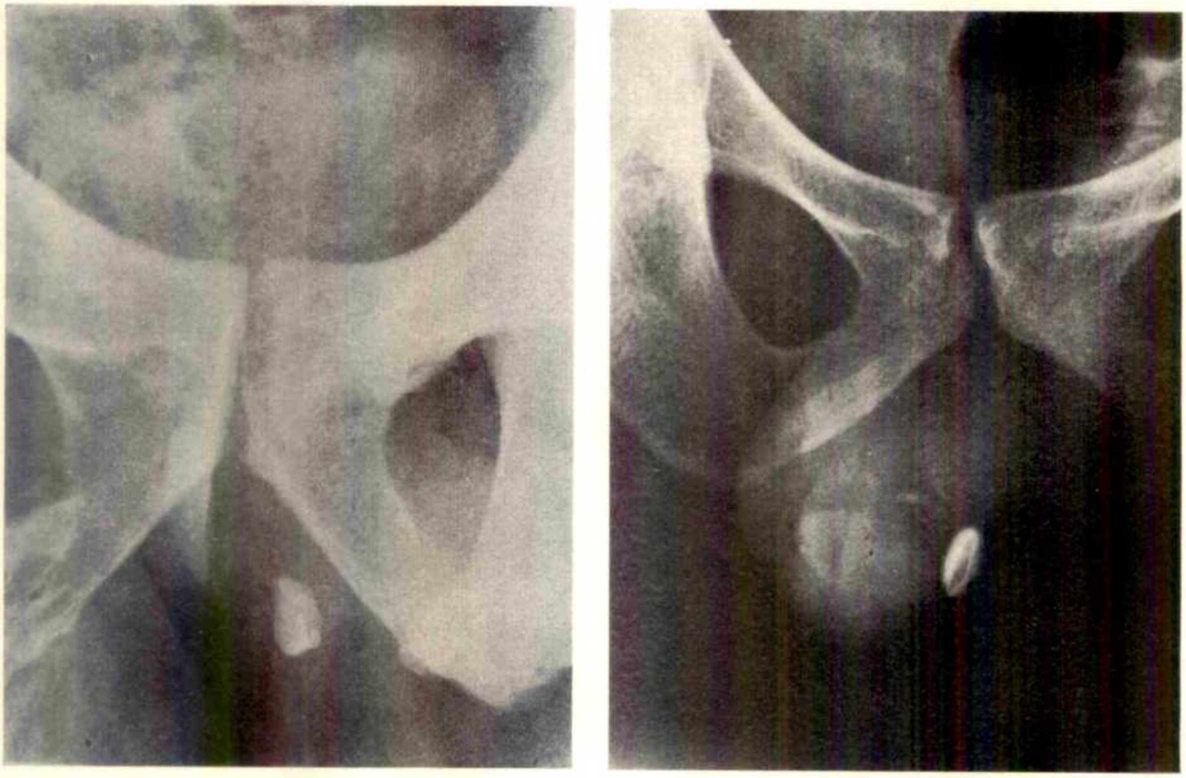
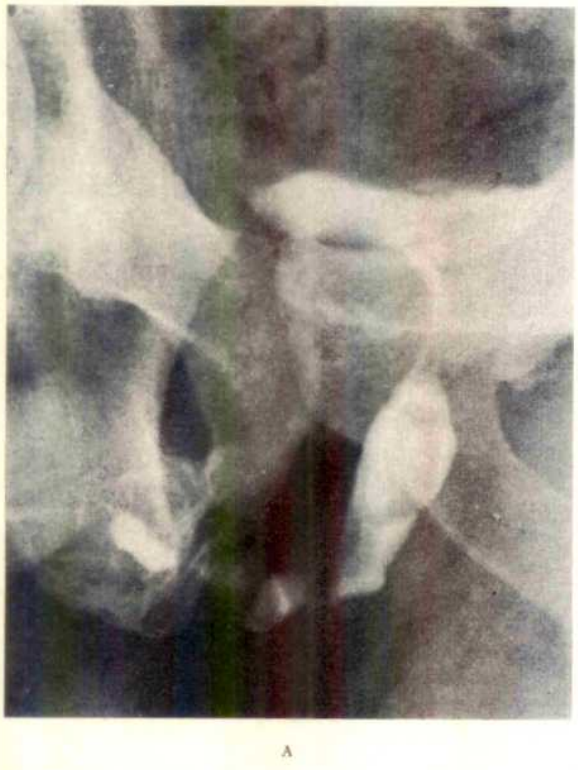

A B

FIG. 1.

(A) Control film of Case 1 showing two opaque calculi. (B) Control film of Case 2, smaller opaque stones are visible.


A

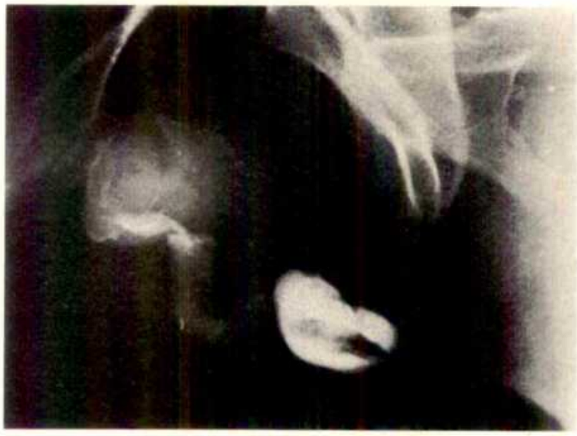

B

FIG. 2.

(A) The post-micturition film in Case 1, outlining clearly the position of the two stones.
(B) The post-micturition film of Case 2.

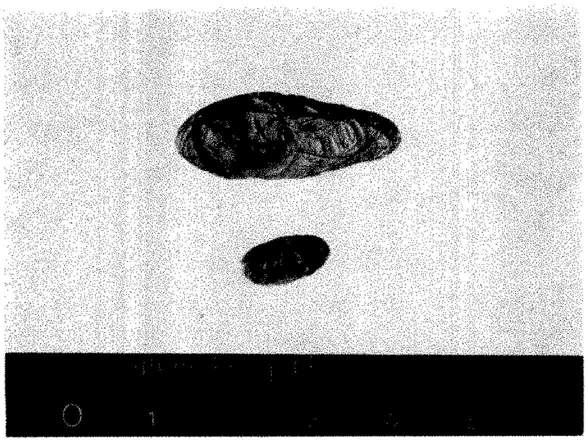


FIG. 3.
The two stones removed from Case 1. The larger stone can be seen to contain embedded hairs.

split skin graft, or a full thickness skin pedicle with its blood and nerve supply. The skin may be from the scrotal area at the base of the penis (Turner-Warwick, 1960; Blandy, 1974), or the hairless region of the prepuce or dorsum of the distal penile shaft (Brannan *et al.*, 1973). Similar urethroplasty techniques have been used to reconstruct the urethra in cases of hypospadias.

Although Brannan *et al.* (1973) have noted the dorsal penile skin to be hairless they claim no advantage for this. Blandy and Singh (1975) suggested that hair-ball formation might be a problem which could develop in the future and associated stone formation has been mentioned (Blandy *et al.*, 1971.) Complications of urethroplasty have been listed as bleeding, stricture-formation, sloughing, bridging, fistula formation (Blandy *et al.*, 1971) and pseudo-diverticulum formation (Turner-Warwick, 1960; Williams and Crawford, 1968; Devine *et al.*, 1968).

There are several methods of performing an ascending study (de Lacey *et al.*, 1973) but before any of these a control film is essential if stones are not to be missed. The after micturition film made the contained stones more easily visible in our patients.

ACKNOWLEDGMENTS

My thanks to Mr. R. H. Whitaker for access to case notes of his patients and his help and advice. The X-ray reproductions and photographs were kindly made by the Photographic Department of Addenbrooke's Hospital. My thanks to Mrs. G. Mack for her secretarial help.

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Mammography in the diagnosis of breast carcinoma: an evaluation of direct referral facilities for family practitioners

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ABSTRACT

An enquiry has been made into the value of direct referral facilities for mammography by family practitioners. This study showed that provided that the limitations of mammography are appreciated, such a system is useful as a contribution to the management of benign breast disease and in the doubtful cases unlikely to have a carcinoma. The number of very early carcinomas discovered has been disappointing and the main use of this type of service has been in reinforcing clinical opinion.

The importance of mammography, as an adjunct to clinical examination, has recently been stressed in connection with mass and selective screening programmes for breast carcinoma (Shapiro, 1975; Chamberlain *et al.*, 1975; Thomas, 1975).

The present study arose out of an enquiry as to the value of this radiological investigation in cancer detection among patients seen in course of everyday family practice, examined clinically by their family practitioner and then referred directly for X-ray examination of the breasts.

The mammography unit at the Royal Surrey County Hospital has, for the past seven years, provided facilities for direct referral from family doctors practising in S.W. Surrey and its surrounds. In 1974 this unit carried out mammograms on a total of 1,796 patients referred from all sources. Of these patients 231 (12.8%) were direct referrals from family practitioners.

Follow-up enquiries, made in respect of each of these latter patients by questionnaires to family doctors, resulted in 195 replies (a response rate of 88.7%) and these provided up-to-date information regarding 184 patients, who are thus the subject of the study.

The two main objectives of the study have been:

(a) To evaluate the usefulness of direct referral facilities for mammography by family practitioners in the diagnosis of breast carcinoma.

(b) To assess, in so far as numbers permit, the diagnostic accuracy of the radiologist's reports on the mammograms.

PATIENTS AND METHOD

The 184 patients included in the study were all female. Eighteen had had mammograms performed prior to 1974 but none had any history of previous malignant disease. The great majority had some clinical evidence of breast disorder but a few were referred on account of cancerphobia, or by reason of a family history of breast carcinoma.

The mammograms were all performed on Medichrome films with low radiation dosage technique (Price and Butler, 1971) and were reported on by a consultant radiologist, who had knowledge of the clinical features at the time of reporting. In instances where high radiographic density of breast tissue rendered interpretation of X-ray appearance more difficult, this was indicated in the reports.

The follow-up was carried out from September 1975 to January 1976, by questionnaires to family doctors and perusal of hospital records.

The patients were classified in accordance with the opinions expressed in the initial radiological reports into four groups:

Group A—probable malignancy
Group B—possible malignancy
Group C—cysts and fibroadenomas
Group D—benign dysplasias and normals

RESULTS

The results of the study are summarized in Table I.

As stressed by Gershon-Cohen (1970), a definitive diagnosis of breast cancer cannot be established without a biopsy. In the 184 patients, there were nine histologically proven carcinomas and one advanced carcinoma in which the clinical and radiological features were thought to establish the diagnosis of malignancy beyond reasonable doubt.

Table II shows that in all ten carcinomas the clinical presentation aroused some suspicion, of varying degree, as to the presence of malignant disease. Fortunately in the one carcinoma (Case 10) found among the 14 patients with radiological features suggesting benign tumours or cysts (Group C), the clinical findings resulted in reference for a surgical opinion and subsequent biopsy revealed an early carcinoma.

Mammography in the diagnosis of breast carcinoma

TABLE I

SUMMARY OF RESULTS

X-ray findings	No. of patients	Nos. referred for specialist opinion	Nos. of biopsies performed	Malignant histology	Benign histology	Nos. referred for F.U. mammograms in 1975
Group A Probable malignancy	8*	8 (100%)	7	6	1	0
Group B Possible malignancy	10	10 (100%)	9	2	7	3
Group C Benign tumours and cysts	14	5 (36%)	4	1	3	2
Group D Benign dysplasias and normals	152	25 (16%)	10	0	10	4
Totals	184	48 (26%)	30	9	21	9

*Includes one patient diagnosed as carcinoma breast on clinical and X-ray evidence only.

TABLE II

SOME DETAILS OF THE TEN BREAST CARCINOMAS

Mammogram	Case	Age	Presentation	U.I.C.C. classification	Treatment
Group A	1	47	L.I.B. (lump in breast)	$T_2N_0M_0$	Surgery
	2	55	L.I.B.	$T_3N_0M_0$	R.T. (Inoperable)
	3	39	L.I.B.	$T_2N_0M_0$	Surgery
	4	43	L.I.B.	$T_2N_0M_0$	Surgery
	5	57	Nipple discharge, breast pain	$T_2N_0M_0$	Surgery and R.T.
	6	61	L.I.B.	$T_2N_0M_0$	Surgery
	7	48	L.I.B.	$T_3N_0M_0$	R.T. Diagnosis on clinical and radiological evidence. No biopsy.
Group B	8	71	L.I.B.	$T_1N_0M_0$	Surgery
	9	71	L.I.B.	$T_2N_1M_0$	Surgery
Group C	10	43	L.I.B.	$T_1N_0M_0$	Surgery

None of the other 13 patients in this group or the 152 patients diagnosed radiologically as having benign dysplasias or normal mammograms (Group D) were found to have carcinomas.

Seven carcinomas were found in the eight patients with X rays showing probable malignancy (Group A). Biopsy on the one false-positive in this group revealed a benign fibroadenoma.

Of the ten patients whose mammograms showed a possibility rather than a probability of malignancy two were found to have a breast carcinoma (Group B).

The total number of biopsies performed was

30 and of these nine carcinomas were found on subsequent histological examination. This biopsy rate is low when compared with screening programme figures (Shapiro, 1975; Chamberlain *et al.*, 1975; Pomerance *et al.*, 1976) and no carcinomas have been diagnosed subsequently in women who did not have a biopsy.

DISCUSSION

When the direct referral mammography scheme for family practitioners was first introduced it was hoped that it would make a substantial contribution to the very early diagnosis of breast carcinoma. Whilst these early hopes have not been realized, the occurrence of two T_1N_0 carcinomas in the ten carcinomas found in this study shows that such a scheme can play some part in furthering this objective.

Statistics from the South West Metropolitan Cancer Registry (The South West Metropolitan Cancer Registry, 1976) show that in 1974, 324 new cases of breast carcinoma were registered from the Guildford group of hospitals. In 311 patients the U.I.C.C. classification was known. The total number of patients with nodal involvement and including the inoperable T_3–T_4 cases was 190 (61.1%) and the total of early T_1N_0 carcinomas was 49 (15.7%) and T_2N_0 carcinomas 64 (20.6%). There were 8 (2.6%) T_3N_0 carcinomas.

These latter figures suggest that in this district and its surrounds the majority of patients with breast carcinoma are referred directly to hospital surgical clinics, by their family doctors. Direct referral for mammography, by these practitioners, would seem to be employed for patients with doubtful or puzzling clinical features and for benign disease. The subsequently reported radiological findings, taken in conjunction with the clinical findings of the family doctor, would thus appear to have an important influence in helping him to assess if an urgent or less immediate specialist opinion is required; to decide on treating the patient conservatively himself—perhaps with subsequent follow up mammograms; or in instances with completely negative clinical and radiological findings to offer the patient reassurance.

Those who use a direct reference system must be fully aware of the limitations of mammography and a firm clinical indication for biopsy must always override a negative X-ray report. This is exemplified by the one false negative in the study (Table II, Case 10) where a histologically proven carcinoma was diagnosed radiologically as a fibroadenoma. Mammography nevertheless may be helpful in confirming the presence of benign dysplasias or cysts, but where there are dubious clinical signs and a normal mammogram, astute clinical judgement and follow up films may be needed to avoid unnecessary biopsy.

The proportion of T_1N_0 and T_2N_0 cases was higher in the family practitioner direct referral series than in those cases referred directly to the hospital clinics. The distribution of T_1–$T_2N_0M_0$ carcinomas in this study has a striking resemblance to the symptomatic patients who presented themselves at a selective screening programme in Guildford and also the symptomatic patients seen in the West London screening programme for breast neoplasms (Chamberlain *et al.*, 1975). Health education programmes may reduce the numbers of advanced symptomatic patients, but it is unlikely that a direct referral system will improve the yield of T_1N_0 cases to the levels achieved in screening programmes (Shapiro, 1975; Chamberlain *et al.*, 1975; Pomerance *et al.*, 1976). Although the number of early carcinomas discovered has been disappointing the main use of this type of service has been in reinforcing clinical opinion for both benign and malignant disease rather than in the detection of early cancer.

ACKNOWLEDGMENTS

We are grateful to Dr. B. J. Loveday for participating in the radiological reporting, Dr. D. O. Williams for advice on the family practitioner's view-point, to Mr. Lionel Taylor and Miss Dawn Pullen of the Guildford Hospitals for help with the radiological and breast clinic records and to all the family practitioners who so promptly replied to our enquiries.

Lastly, we wish to express our appreciation to all the radiographers whose interest and enthusiasm resulted in the production of consistently high quality radiographs.

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A simple computer program for optimization of source loading in cervical intracavitary applicators

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ABSTRACT

A computer program has been developed to aid in the brachytherapy of cancer of the cervix. Using a least-squares minimization algorithm, the program will optimize the source loading in intracavitary applicators so as to reproduce, as nearly as physical considerations allow, the dose distribution requested by the user. Applicator geometry and the relative positions of anatomical points of interest must be supplied to the program, as well as an inventory of available source strengths. Output from the computer includes the optimized source loading, time of application, and the resulting relative doses to the various user-selected points of interest.

Memorial Hospital makes extensive use of computers in planning the radiation treatment of its cancer patients. In particular, in brachytherapy of cancer of the cervix, a PDP 11/45 computer is used to calculate the absorbed dose delivered to specified points in the body by afterloaded radium sources. The sources are located in an intracavitary applicator which has previously been inserted into the uterus and vagina. The positions of points of interest in these organs and surrounding tissues, as well as the positions of dummy sources in the radium applicator, are determined from radiographs taken of the patient soon after the applicator has been inserted. A typical case is illustrated in Fig. 1, which represents a radium applicator *in situ* as viewed on an antero-posterior radiograph. Four dummy radium sources are in the central uterine tube and one source is in each of the vaginal tubes. Also shown are some of the points of interest used at Memorial Hospital: REF$_{\mathrm{R}}$, REF$_{\mathrm{L}}$ (the standard reference points "A"); CVX$_{\mathrm{R}}$, CVX$_{\mathrm{L}}$ (right and left cervix points); VAG$_{\mathrm{R}}$, VAG$_{\mathrm{L}}$ (vagina surface); and UTE$_{\mathrm{R}}$, UTE$_{\mathrm{L}}$ (uterus).

The general procedure followed at Memorial has been for the medical physicist, in accordance with objectives determined by the radiotherapist, to guess at a suitable source loading, obtain a computer print-out of the corresponding dose pattern and then intuitively modify the loading, if necessary, to improve that dose pattern. This trial-and-error procedure usually took anywhere from 15 min to two hours, depending on the difficulties presented by the patient's anatomy and clinical considerations. The essential problem was that, with anywhere from three to seven sources being inserted and with the desired dose to perhaps 15 points of interest being specified, it was by no means obvious which source strengths might be varied, and by how much, to bring about an overall improvement in the dose distribution due to a particular trial source loading.

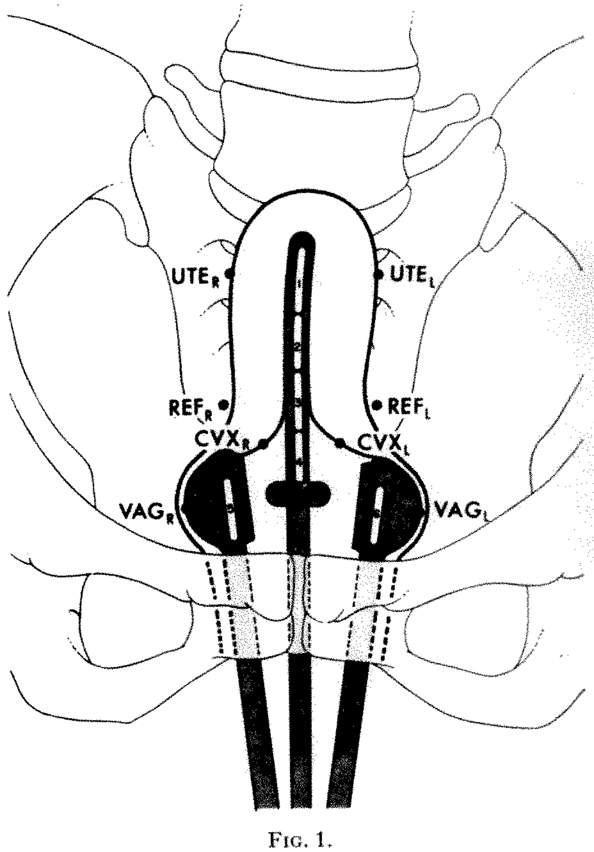

FIG. 1.

Intracavitary applicator with dummy sources as seen in an antero-posterior radiograph. Also shown are some of the points of interest used at Memorial Hospital. (Figure supplied by Dr. B. Hilaris, Memorial Hospital.)

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This article describes a new computer program which has been written to optimize the source loading for cervical intracavitary applicators. By solving the problem described above it frees the physician, or user, from being overly concerned with the details of loading and permits him to concentrate on the more fundamental question of desired dose distribution. Furthermore, the program can help clarify to the user any correlations that may exist between the doses delivered at various points of interest. It also may indicate, for example, the need to increase the inventory of available source strengths. Since it was intended for clinical use rather than research, the following attributes were considered necessary:

(a) speed;
(b) simplicity of operation;
(c) output only of realistically possible loadings;
(d) suggestion of alternative loadings;
(e) indication of how well the resulting dose distribution matches the desired one; and
(f) structure sufficiently general to permit adaptation to new treatment modalities and techniques.

We will first discuss individually each of these requirements and later present a description of the program's input and output.

ATTRIBUTES OF THE PROGRAM

(a) *Speed.* Since the entire process of finding a final, optimum source loading requires much interaction between the program and the user, it is clearly desirable to keep to a minimum the user's waiting time for computer results. Using this program at Memorial Hospital on the PDP 11/45 computer, the optimum loading is typically printed out in a few seconds, after consideration of perhaps 50 or more possible combinations of source strengths.

(b) *Simplicity.* Input requirements were kept to a minimum and the input format was made self-explanatory in order to permit persons not having specialized computer training to operate the program once the general procedures and associated computer programs had been set up.

(c) *Realistic loading.* To prevent the program from suggesting a source strength not available in the department, a radium source inventory is inserted into it and only those source strengths listed therein are considered. A strength of zero is allowed and would represent a dummy source.

(d) *Alternative loading.* Alternative loadings are desirable in situations where certain source strengths are in short supply due to radium treatments already in progress. Also, in a particular case the physician may find it difficult to express his dose distribution requirements in terms of his usual reference points and will be interested in seeing "reasonable" alternatives to the optimum he has explicitly requested.

(e) "*Goodness*" *of distribution.* As a quantitative measure of this quantity the program prints out, with each source loading, a number related to the deviation of the dose at each point of interest from that requested. This number is useful in comparing alternative source loadings.

(f) *Generality.* In order to be useful to hospitals other than Memorial, the program itself is not bound to any particular applicator technique. Both the points of interest for dose optimization and the available source strengths are defined by the user.

OPERATION AND DETAILS OF THE PROGRAM

Input

The input to the program may be divided into two types. The first pertains to the "patient system". That is to say, the relative positions of the points of interest with respect to the sources (all assumed to possess the same physical dimensions) in their applicator must be determined. This permits computation of the effect of each source on the dose at each point. In order to allow use of the program for varying patient systems these auxiliary calculations are performed separately. Thus, upon execution, the program reads in a computer file which contains a table of the dose rate delivered to each reference point by each source individually, assuming unit source strength. At Memorial Hospital this file is produced by the program BRACHY (Mohan, 1975). It is this table which supplies all necessary facts concerning a particular case, including the points of interest chosen by the user. It is essential that a sufficient number of appropriately located points be chosen to represent adequately the desired dose distribution.

The second type of input involves data which will, in general, be entered by the user at execution time, although initial values are stored in the program. These data include the actual dose desired at each point of interest together with its relative importance, or weighting factor. The latter is necessary since compromise is inevitably required and the program must be told which restrictions to relax for the sake of others. In addition to the dose at each point, the average dose rate to the first two points of interest is also optimized. Typically, these would be chosen to be the standard points "A" generally referred to in treating cancer of the cervix.

Optimization procedure

The basic method of optimization is to minimize the function

$$R = \sum_{i=1}^{n} w_i (d_i - o_i)^2$$

where (except for i=1 and 2) w_i is the weighting factor for the ith point of interest, d_i is the ratio of the dose rate at point i to the dose rate at a chosen point of reference and o_i is the ratio of the optimum dose desired at point i to that at the reference. The reference point, designated by the user by assigning a negative weighting factor to it, will necessarily have exactly its desired dose since it is the dose-rate at this point which determines the treatment time, after the relative dose distribution has been optimized.

As noted above, the first two terms in the function R are different from the others. In the first, d_1 is the average dose rate to the first two points of interest and, in the second, d_2 is the average dose to those same points divided by the dose at the reference point. Generally these two points of interest, always treated as a pair, would be chosen to be the points "A" previously mentioned.

To begin the optimization, a trial loading must be supplied by the user. It is advisable, though not necessary, that a realistic combination of source strengths be chosen since the program finds only a local, rather than absolute, minimum of the function R. While this circumstance may be incomplete from a mathematical point of view, it has been found to be of little consequence in practice.

Given a trial loading, the program then optimizes the loading by computing R for various combinations of source strengths and accepting that loading which minimizes the function. Specifically, each source strength is replaced, one at a time, by consecutively increasing values until R is found to increase. When R has thus been minimized by varying a particular source, the program goes on and repeats the process with the next source. After all sources have been optimized in this manner we say that one iteration has taken place. The entire procedure would then be

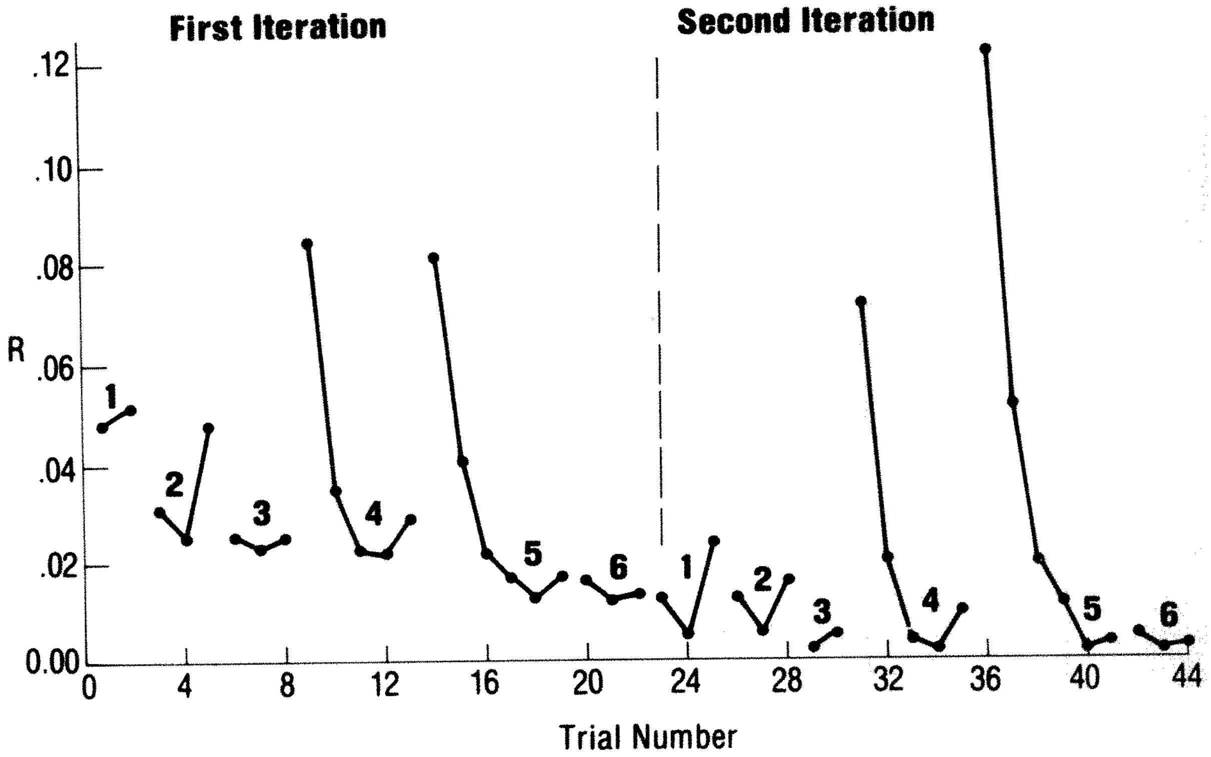

FIG. 2.

Plot of the function R versus trial number in an optimization of six source strengths for two iterations. Each curve represents the variation in strength of a single source whose position number (see Fig. 1) is shown with it. The inventory of available source strengths includes 0, 5, 10, 12.5, 19.5 and 25 mg of radium.

FIG. 3.

Partial output from a typical run of the program.

```
HOW MANY ITERATIONS?  3
1         0.012706        5.0         19.5        12.5        5.0         5.0         0.0
2         0.002248        5.0         19.5        12.5        0.0         5.0         5.0
3         0.002248        5.0         19.5        12.5        0.0         5.0         5.0
NORMALIZATION DOSE=3000./3000.  TIME=50·89 HOURS  RATE=58·95 RAD/H
REFR      REFL      CVXR      CVXL      OBTR      OBTL      VG5R      VG5L      VAGR      VAGL
102.0     98.0      202.2     190.2     21.2      23.2      52.2      59.6      95.4      112.2
REC1      REC2      REC3      REC4      REC5      SIG       BLDC      BLDS      FLNG
31.5      29.6      28.2      25.2      22.1      41.6      40.5      64.6      122.8
UTER      UTEL
71.7      76.1
```

repeated until two consecutive iterations produce the same loading, following which the associated dose distribution is printed out together with other relevant parameters.

The need for the above-described cut-off each time R increases is clear from the fact that a case in which seven sources are to be loaded, each having any of six possible values, would otherwise require that nearly 280000 combinations be tried. As it is, a typical program run of four requested iterations would try 50–100 combinations and takes about five seconds on the PDP 11/45 system.

The steps taken in an actual optimization run of two iterations are represented in Fig. 2. To begin, all sources have their initial values, except for source #1 which is assigned its minimum possible strength of zero. The function R is computed, source #1 is re-assigned to the next available strength (5 mg) and R is then determined again. Since the second value of R is larger than the first, source #1 is fixed at its first trial strength (0 mg) and the computer proceeds to vary source #2. Now (trial #3) sources 3 through 6 retain their initial strengths, source #1 has its optimized value of 0 mg and source #2 is set to its lowest possible value of 0 mg. The trial-and-error procedure continues automatically for all six sources. After one complete iteration (trial #22) the program then returns to the first source and begins varying strength again, each source now having its initial strength replaced by the optimized one determined in the previous iteration. Note that the second iteration improved on the first by changing the strengths of the first and third sources. Figure 2 also illustrates the fact that R exhibits only one minimum as a function of any one source strength when all other source strengths are held fixed. This condition is fundamental to the validity of our cut-off procedure and may be proved mathematically.

Output

A partial print-out from a typical run of the program is shown in Fig. 3. We note that the value of the minimization function R and its associated source loading are printed out for each iteration requested, in this case three. For the last iteration, the average dose-rate to the first two points of interest, as well as the total time of radiation necessary to deliver the full normalization dose to the points receiving it, are also given. Finally, the computed dose to all points of interest (see Fig. 1), as a percentage of the normalization dose, is supplied, along with user-assigned names for each point.

SUMMARY AND CONCLUSIONS

This article describes a computer program designed to compute the optimal source loading for cervical intracavitary applicators. The method is to try various possible source strength combinations and then choose the one giving the lowest value of the function R, which is determined by the deviations of the dose at selected points of interest from the dose desired.

It is hoped that, aside from reducing the time of the decision-making process, this program will also help to improve treatment by allowing the physician to select the actual dose he wants delivered to various locations in the treated region.

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Effects of radiation on the visual appearance and mechanical properties of mouse skin

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ABSTRACT

A study of the long term effects of radiation on the visual appearance and mechanical properties of mouse skin is presented. The effects associated with the hair follicle (greying and alopecia) increase monotonically with exposure. Other effects (load, extension and stress at rupture and scarring of the skin) all show a reversal at the highest exposures. The skin thickness changes little with exposure, while the skin stiffness exhibits a shoulder on the response curve. Possible mechanisms underlying these effects are discussed.

This paper aims to establish a method for studying the cosmetic effect, on the skin of mice, of single X-ray doses similar to those used clinically. We have combined visual scoring techniques and objective measurements of the mechanical properties of the skin. In the natural process of aging the skin becomes thinner and wrinkled and often becomes dry and leathery. A correlation between age and the elastic properties of skin has been shown in both the human (Dick, 1951; Jansen and Rottier, 1958; Wells, 1954) and in the rat (Fry *et al.*, 1964); old skin is less resilient and less extensible than young skin. Chronic exposure to ultraviolet rays accelerates the aging process in skin (Howell, 1960; Knox *et al.*, 1962; Smith *et al.*, 1962) and has been shown to alter its elastic properties *in vitro* (Lovell, 1973). Similar effects on skin have been noted after X irradiation. We have therefore measured the elastic properties of mouse skin at intervals after X irradiation.

MATERIALS AND METHODS

Male C$_3$H mice approximately ten weeks old and 20 g in weight had the flank hair plucked to ensure that the hair follicles were in the same state of the growth cycle at the time of irradiation three days later. The mice were then placed in a cellophane harness in which windows had been cut, and two areas on each flank within the previously plucked region were irradiated without anaesthesia. The radiation was given at 50 kV, 25 mA with 1.0 mm Al filter, 5 cm focus skin distance, and half-value thickness 0.77 mm Al. Two areas were irradiated on each mouse on the anterior and posterior of the same flank using a cone of 1 cm diameter.

The exposure rate was measured each time the mice were irradiated; it varied around 3800 R/min. Exposures of 1500, 2500, 3500 and 4500 R were given. These represent the range of accumulated doses relevant in radiotherapeutic treatments. The depth of the hair follicle below the skin surface three days after plucking is 230 μm (Burlin *et al.*, 1968). The depth-dose relationship shows that the dose at the follicle base is 98% (*Brit. J. Radiol., Suppl. 11*, 1972) of the incident dose. The back-scatter factor for a 1 cm diameter field is 1.00 at this quality (*Brit. J. Radiol., Suppl. 11*, 1972) and the value of rads per röntgen is 0.90 (International Commission on Radiological Units and Measurements, 1962). The calculated dose to the hair follicle base is therefore 0.88 rad per röntgen of exposure at the skin surface.

Since the investigation was designed to study the long term if not permanent effects of radiation on the skin, observations were made several months after exposure. Previous work on the effects of X rays on the regrowth of hair in the mouse (Burlin *et al.*, 1968; Burlin *et al.*, 1973) has indicated that, after approximately three months from completion of the irradiation, the response has reached a stable level and little if any further recovery occurs. Therefore the mice were observed at 89 and 166 days after irradiation. The state of the hair coat in the irradiated area was assessed relative to that of the unirradiated part of the flank. The method of scoring is summarized in Table I. The scoring was made by at least three independent observers. The different observers usually gave the same score, but such differences as did occur seldom exceeded ±1. When necessary the scores of the three observers were averaged and rounded off to the nearest integer. At the same time the percentage of grey hairs within the area was estimated visually by the three observers and the average percentage calculated. In this estimation the peripheral hairs, which may have been situated in the penumbra of the X-ray field and therefore subjected to a smaller dosage, were ignored.

At the same time the skin condition was also observed by at least three observers, the method of

TABLE I

Method of scoring the coat condition

Score	State of coat
5	Complete epilation
4	About 10 to 15 hairs present in the irradiated area
3	More than 15 but less than half the number of hairs present, as compared with the unirradiated coat
2	An obvious reduction in number of hairs, but more than half the hairs present, as compared with the unirradiated coat
1	A just perceptible reduction of hairs, as compared with the unirradiated coat
0	No perceptible difference in number of hairs from the unirradiated coat

TABLE II

Method of scoring the skin condition

Score	State of skin
4	Gross damage—deep, depressed scab or scar
3	Moderate damage—scab or scar but only slightly depressed
2	Slight damage—traces of scab or scar, flakes or slight cracks
1	Very slight damage—only just detectable, different from normal
0	Normal
+1	Damage over 80% or more of the irradiated area
−1	Damage over 20% or less of the irradiated area

scoring being shown in Table II. If the extent of the damage was over 80% of the irradiated area the score was raised by one and if it was below 20% of the area the score was lowered by one. Erythema and ulceration had completely subsided at the time of the observations, so this method of scoring was deemed appropriate for long term effects.

At 210 days after irradiation the animals were sacrificed and a section 1 × 2.5 cm cut from the skin of each animal such that the central section exactly embraced the 1 cm diameter circle of irradiated skin. It was noted, at the time the specimen was cut, that there was complete alopecia in the irradiated area. This hairless area was 1 cm in diameter, from which it was concluded that no contraction of the skin had occurred due to irradiation. A similar section was cut from an unirradiated portion of the mouse flank and then all specimens were stored in normal saline before subsequent mechanical testing.

The tests were carried out on a Mayes hydraulic servo-controlled testing machine. The load-extension curves of the skin specimens were recorded on an X–Y plotter. The skin specimen was mounted in two specially designed jaws which have matching blunt serrations to facilitate gripping but to prevent cutting. The lower jaw and a Perspex immersion tank were attached to the main hydraulic actuator. The tank enabled the test to be carried out in saline, since the mechanical properties of skin were dependent on the state of hydration.

The thickness of the skin removed was measured with a Mercer gauge. The gauge very lightly compressed the skin on measurement, giving slight inaccuracy in the measured value of absolute thickness, though the relative measurement was estimated as ±5%. The skin specimen was clamped in the jaws which were set to give a gap of 1 cm. The Perspex immersion tank was filled with saline solution kept at 37±0.5°C and the specimen was allowed to equilibriate in the fluid. A tensile load at an extension rate of 0.25 mm/s was imposed on the skin sample. This extension rate was selected on the basis that skin *in vivo* recovers at this rate, if stretched to blanching. The skin was stretched to rupture and the load extension characteristics were recorded. For each specimen the following mechanical properties were measured:

1. the skin thickness;
2. the load at rupture;
3. the extension at rupture;
4. the mechanical stress at rupture. This was calculated from the load at rupture divided by the cross sectional area of the specimen;
5. the stiffness.

The final part of the load extension curve is primarily associated with the stretching of the aligned collagen fibres. This property will be referred to as the stiffness of the skin and is defined as slope of the last quarter of the load extension curve, $\Delta F/\Delta E$. In order to give the property units (N/mm^2) and meaning consistent with other values of stiffness, the values of original length, L, and cross-sectional area, A, are brought into each calculation through the equation

$$\text{Stiffness}=\left(\frac{\Delta F}{\Delta E}\right)\frac{L}{A}$$

where F is the load and E is the extension.

Results

Observations made at 89 and 166 days confirmed that there is very little change between these times (see Fig. 1 where the coat condition is plotted against the radiation exposure). In this figure the mean scores for each group of mice are presented for the

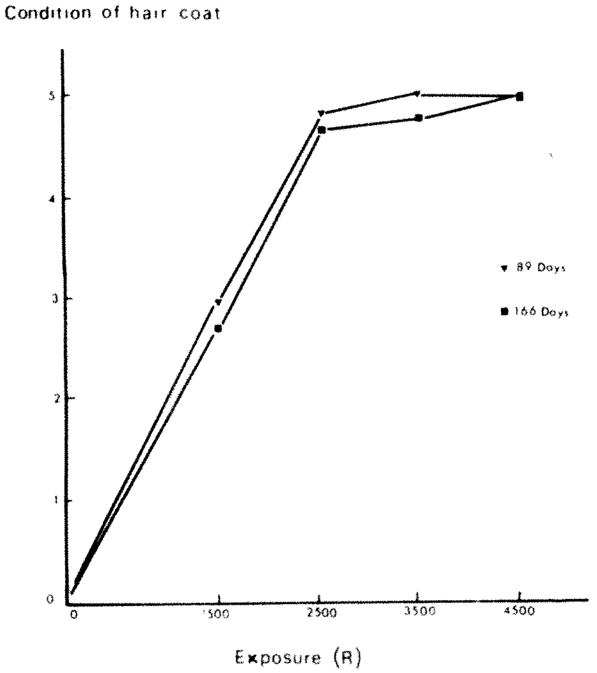

FIG. 1.
Variation of the condition of the hair coat with exposure.

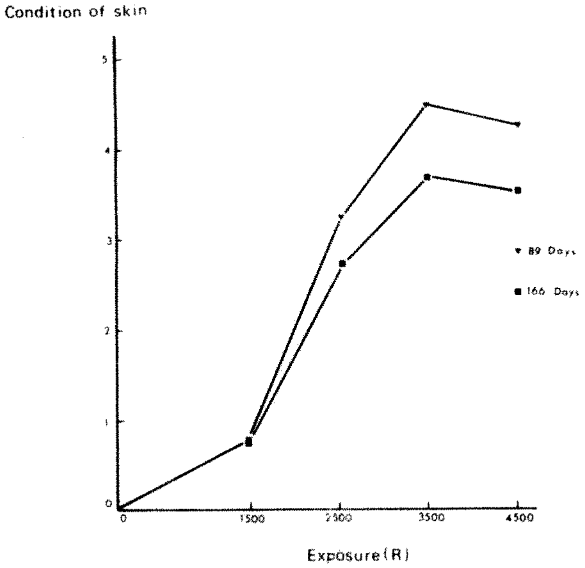

FIG. 2.
Variation of the condition of the skin with exposure.

two time intervals after radiation. The highest doses induced complete alopecia. For all doses there is minimal difference between the state of the coat at the two periods after radiation.

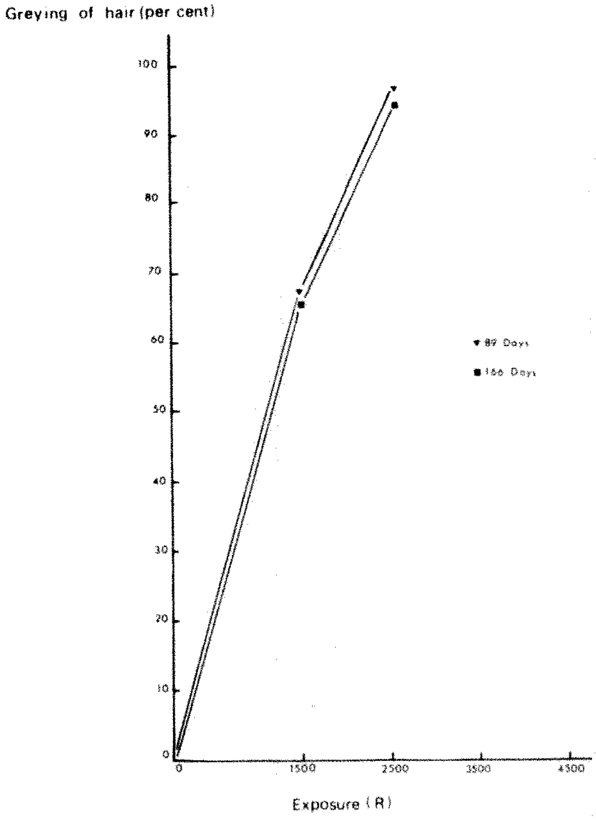

FIG. 3.
Variation of the percentage of grey hairs with exposure.

In Fig. 2 the skin condition is plotted against exposure at both time intervals after irradiation. The results followed a sigmoid response curve which is frequently encountered with radiation effects. There is some evidence of recovery between 89 and 166 days with the higher doses of radiation, though this is slight. The results suggest that at the highest dose the permanent damage to the skin is slightly less than that which occurs at the next highest exposure (3500 R). Similar effects have been observed in other experiments on skin by Fowler and Denekamp (personal communication).

The use of greying of the hairs as a criterion of radiation damage was less satisfactory in that it is inapplicable when complete alopecia occurs. This system would be more appropriate at lower exposure levels than used here. If coupled to the degree of alopecia as presented in Fig. 3 it could provide a scoring system over a very wide range of radiation exposure.

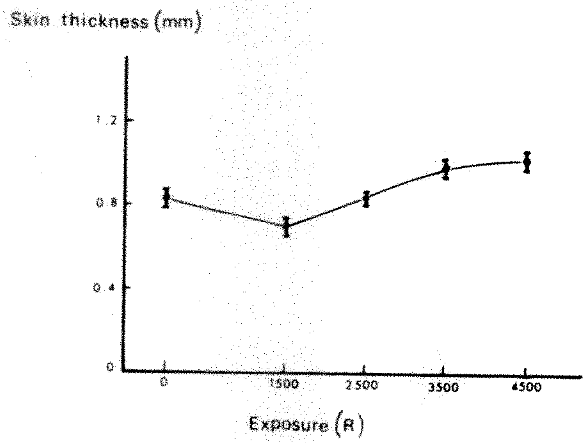

FIG. 4.
Variation of the skin thickness with exposure 210 days after irradiation

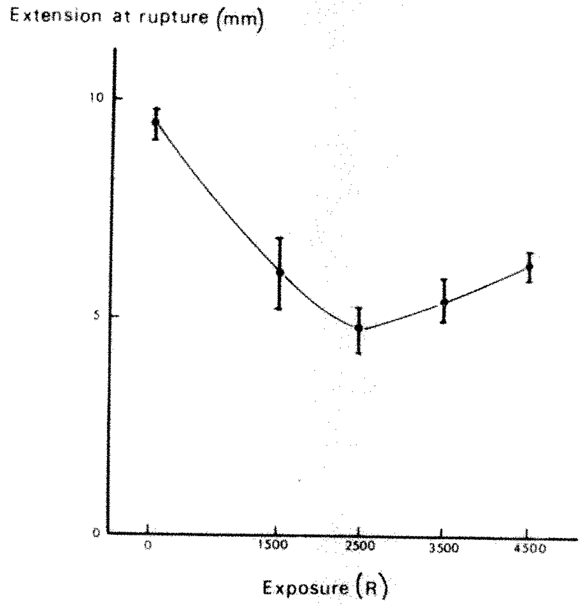

FIG. 6.
Variation of the extension at rupture with exposure 210 days after irradiation

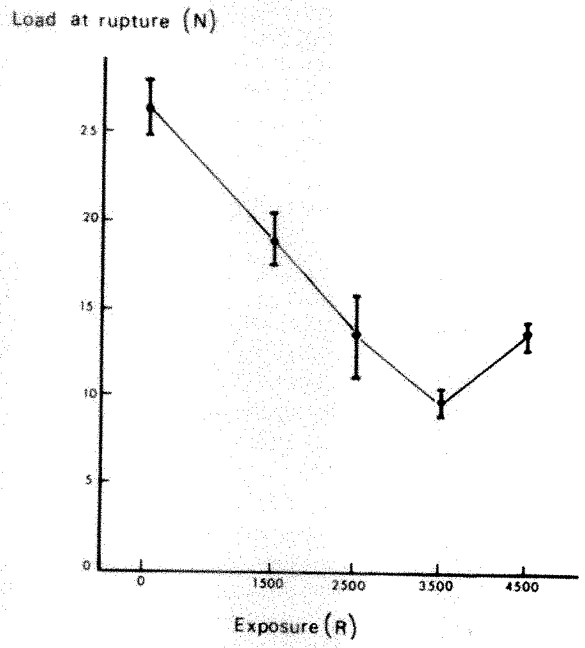

FIG. 5.
Variation of the load at rupture with exposure 210 days after irradiation.

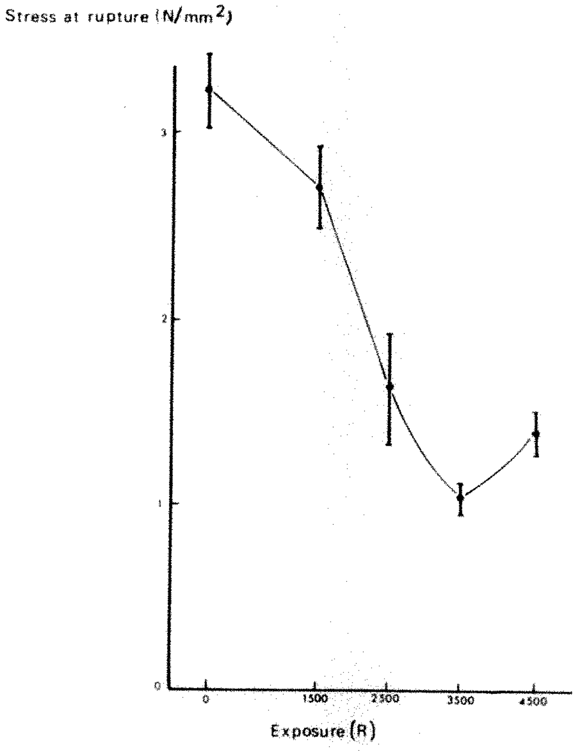

FIG. 7.
Variation of the stress at rupture with exposure.

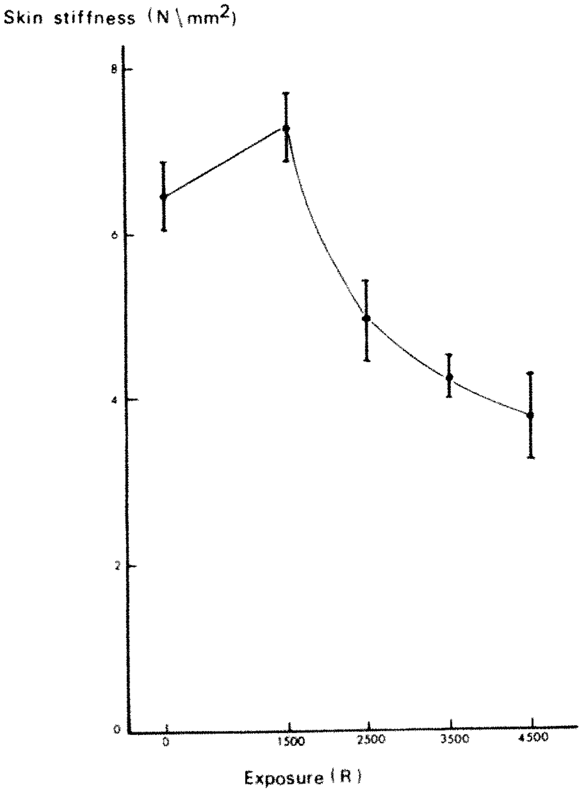

FIG. 8.

Variation of the skin stiffness with exposure 210 days after irradiation.

The thickness of the skin 210 days after radiation is presented in Fig. 4. There is a small but nevertheless significant increase with X-ray exposure. Similar results have been found in rats, namely that the thickness does not vary with the time interval after radiation at least from 50 days onwards (Ranu *et al.*, 1975). The variation of the load at rupture with exposure is presented in Fig. 5. It will be noted that, as in the case of the visual assessment of skin damage, there is a reversal in the response; the load required to rupture the skin decreases up to 3500 R but then increases at 4500 R. Similarly, a reversal at the higher doses is seen in Fig. 6 where the variation of the extension at rupture with exposure is presented, but in this case the minimum occurs at 2500 R. In Fig. 7 the stress at which rupture occurred is plotted against exposure, again showing a reversal of the curve at the highest dose. This reflects the reversal in the load curve shown in Fig. 5 since the skin thickness varies little with exposure.

The skin stiffness is plotted against exposure in Fig. 8. After an initial shoulder the stiffness shows a marked dependence on dose. This shoulder phenomenon is frequently observed in other radiobiological responses. The general trend is very similar to the dependence on dose of stiffness of rat skin (Ranu *et al.*, 1975).

DISCUSSION

In order to develop a method of assessing the cosmetic appearance of skin and its appendages, several very disparate end-points have been examined. Cosmetic acceptability is subjective and therefore visual attributes such as alopecia, greying of hair, and scarring of skin have been scored on a numerical system as explained. The utility and function of skin, and possibly also its cosmetic appearance, will bear some relation to its mechanical properties and these have also been examined using a variety of criteria.

It is of interest to note how very different end-points such as the visual appearance of the scarring of skin and the load, extension and stress at rupture all show a similar reversal at the highest exposure (*i.e.* the response for each end-point is less at 4500 R than at 3500 R). But this does not apply to changes in the hair, either the absence of hair-growth or its greying. The two sets of stem cell population in the case of hair growth and greying are fairly specifically located in the base of the hair follicle, which three days after plucking is at a depth of about 230 μm, while the relevant cell population for damage to the skin is much more widely distributed. The differences in the dose response function noted between skin and hair may therefore reflect differences in the nature, radiosensitivity, cell kinetics and location of the relevant cell populations.

The reversal effect noted with several of the end points related to the condition of the skin and its mechanical properties is not unknown in radiobiology. For example, in carcinogenesis the probability of inducing a cancer depends on the probability of first inducing a malignant change within a cell and secondly on the probability of that cell surviving. At higher doses cell killing effects often reduce the probability of cancer induction, in that fewer of the cells in which malignancy has been induced survive. A similar interpretation is possible in the case of these experiments. At low doses certain changes are induced in stem cell populations which manifest themselves as increased scarring or a decrease in the load, extension and stress at rupture, whereas at higher doses of radiation cells that would only have been damaged at lower doses fail to survive.

Alternatively the highest exposure (4500 R) may have killed the stem cells sufficiently to allow an ingrowth of normal skin from the surrounding tissue. Electron microscope studies in rats (Ranu *et al.*, 1975) indicate that after high doses of radiation the collagen changes from a fibrous structure to a much more matted structure with extensive cracks. This type of material would have been bounded by relatively normal skin had such ingrowth occurred at the highest doses and reversal would be explained by the fact that the measurements were made on a composite specimen. Although an ingrowth was not visually apparent, it may have occurred at a subepidermal level.

The end points of hair re-growth and hair greying, neither of which exhibited any reversal effect with increasing dose, reflect the action of radiation on different cell populations, and the nature of these end points is also qualitatively different. The presence or absence of a hair or of colour may be manifestations of cell killing and not of the quality of hair produced by the survivors. If this is so, no reversal of radiation response would be expected.

It is suggested that a six month period in the mouse is comparable to a much longer period in man. The method we have described has an advantage in that low energy X rays can be used conveniently. It is concluded that the method is a suitable model for studying the cosmetic effects of irradiation and can be used to investigate the relative merits of different fractionation schemes employed in the treatment of malignant disease of the skin.

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The response of tissues to combined hyperthermia and X rays

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ABSTRACT

Three normal tissues in mice and rats (skin, intestine and cartilage) have been used to investigate the effects of combined hyperthermia and radiation. The heating time was kept constant at one hour and X rays were given either immediately before or after heating. Thermal enhancement ratios were measured as a function of temperature up to 43°C and were compared with data for other normal tissues and tumours taken from the literature. The variation from tissue to tissue was found to be fairly small within this temperature range, but there is some indication of a greater response of tumours.

Hyperthermia was first used in the treatment of cancer more than 100 years ago. Since then there have been periods of renewed interest, but a considerable impetus was provided by the work of Cavaliere and his colleagues (Cavaliere *et al.*, 1967), who showed that animal tumour cells were damaged by heat to a greater extent than normal cells.

In addition to killing cells, heat also potentiates the effects of ionizing radiations and certain drugs. The crucial question in regard to the clinical use of hyperthermia, however, is whether the effects of heat alone or in combination with other agents are greater on neoplastic tissues than on their normal tissue counterparts. Some reasons for believing that this may be so have been derived recently, mainly from experiments *in vitro*, and these are given below:

(1) Hypoxia does not protect cells from damage by heat alone and may even be a sensitizer (*e.g.* Gerweck *et al.*, 1974). If hyperthermia is combined with X rays, the protective effect of hypoxia is much less than with X rays alone (Robinson *et al.*, 1974a).

(2) Nutritionally deprived cells, which probably exist in many tumours, are more sensitive to heat than adequately fed cells (Hahn, 1974).

(3) Neoplastic cells may be intrinsically more sensitive to heat than their normal counterparts (Cavaliere *et al.*, 1967).

(4) Heat may be more damaging at low pH (Overgaard, 1977) and it is commonly thought that tumours tend to be acidic due to anaerobic metabolism.

(5) Heat is more damaging to cells synthesizing DNA. This is during the part of the cell cycle (S phase) where X rays are least effective (Westra and Dewey, 1971). There is therefore a difference between the two modalities, which may be useful for treatment of tumours in which more cells are in S phase than in the limiting normal tissues.

(6) If the heating is localized, tumours with a poor blood supply may attain a higher temperature than the surrounding normal tissues. Even a small temperature difference could be most important.

Human tumours have now been treated by heat alone and some excellent results have been reported (Stehlin *et al.*, 1975). However, most patients benefited only by a temporary remission with subsequent recurrence (*e.g.* Pettigrew *et al.*, 1974). Heat combined with cytotoxic drugs or X rays or both together may be a more useful treatment, but it is necessary to obtain further information on the effects of such combinations before patients are exposed.

It is known from many studies in radiation biology that the quantitative response of tissues *in vivo* is not necessarily the same as that for cells *in vitro*, so it is necessary that hyperthermia studies be performed on tissues *in situ*. The present work is an attempt to measure the response of three tissues in rodents to combined heat and X rays, namely cartilage, intestine and skin. Heating for one hour with a range of temperatures up to 43°C has been used and given either immediately before or after irradiation. Thermal enhancement ratios (TER), defined as the dose of X rays alone divided by the dose of X rays with heating to produce the same given level of damage, have been measured as a function of temperature for the three tissues and are compared with values derived from published data for other normal tissues. There is also a limited amount of data for tumours available in the literature and these are compared with those for the normal tissues.

METHODS AND RESULTS

Methods of heating and irradiation

In all cases heating was by means of immersion in hot water. A thermostatically controlled water bath was used with a temperature variation not greater than 0.05°C. Irradiation was given with 250 kV

X rays, HVL 1.2 mm Cu, at a dose rate of 3.6 Gy/min for skin, and 1.8–1.9 Gy/min for cartilage and intestine. Seven-day-old rats were anaesthetized by intraperitoneal injection with sodium amylobarbitone at 0.07 mg/g body weight and mice with pentobarbitone sodium (Sagatal) at 0.065 mg/g body weight. Animals were always allowed to recover in a warm box.

Cartilage

Growing cartilage has been used previously as a system for assessing the effects of radiation on normal tissue by measuring the stunting of growth in the tail vertebrae of baby rats (Wright and Howard-Flanders, 1956; Dixon, 1967). This technique was used to investigate the effects of heat and radiation.

Only the portion of the tail distal to vertebra No. 10 was treated. In this way, the mean length of a group of vertebrae in the untreated portion could be compared with the mean of a group in the treated portion and a percentage stunting obtained for each rat. The vertebrae measured were numbers 6, 7 and 8 in the untreated portion, and 12, 13 and 14 in the treated portion. Stunting is defined as $\left(1-\frac{r}{R}\right)\times 100$ where

$$r=\frac{\text{average length of vertebrae 12, 13 and 14}}{\text{average length of vertebrae 6, 7 and 8}}$$

in irradiated rats and R is the same quantity in control rats. The tails of seven-day-old CFHB rats were immersed in the warm water to the level of a mark made on the tails at the position of vertebra 10, *i.e.* 0.6 of the length of the tail from its tip. The internal temperature of the tails during heating was measured using thermocouples, and was found to rise to 0.1°C below water bath temperature within seconds. The temperature in the tail immediately above the water surface, however, rose slowly and never to more than 37°C at a water bath temperature of 43°C.

Heat was applied for one hour immediately before irradiation, with a delay of three to four minutes between the treatments. After treatment, the animals were allowed to mature, and at 13 weeks, when growth was complete, the tails were radiographed and the lengths of the vertebrae measured.

No qualitative differences have so far been observed between the damage caused by heat plus X rays and that caused by X rays alone. In the range of temperatures used in these experiments, heat alone had no measurable effect at 42°C for one hour. 43°C for one hour produced 10%, 6% and zero stunting in three separate experiments. The mean value of about 5% is approximately equivalent to an X-ray dose of 3.0 Gy.

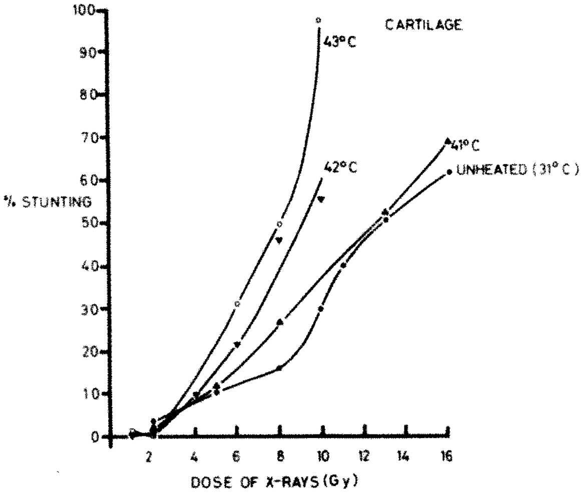

Fig. 1.

Dose response curves for damage to baby rat cartilage which had been heated to various temperatures for one hour immediately before irradiation. The response used was the percentage stunting of the vertebrae for treatment of half the tail.

The dose effect curves obtained are shown in Fig. 1. No thermal enhancement of X-ray damage was obtained after heating at 41°C, but at 42°C a TER of 1.4 was obtained at the 50% stunting level, and 1.6 at 43°C (Table I). Heat given after irradiation was rather less effective in one experiment at 43°C, amounting to a reduction in TER of about 10% (Myers and Field, 1976).

Skin reactions

Skin reactions of the mouse pinna were observed for two months after treatment, using female CFLP mice at two months old. Irradiations were performed by placing each animal on its side with its right ear in a collimated X-ray beam. For heating a series of countersunk holes were cut in a 6 mm sheet of Perspex which was supported so that the smallest diameter was at the surface of the water. The mice were Sellotaped in position onto this sheet with only their right ears protruding through the holes and into the water. This procedure resulted in no increase in body temperature (the rectal temperature being 34°C at a water temperature of 41.5°C). In order to maintain anaesthesia for one hour it was necessary to give a second dose of anaesthetic of 0.03 mg/g. Ears were irradiated without heat treatment or heated for one hour after irradiation. Four to six mice were used in each group. The acute skin reactions were scored using the system given in

TABLE I

Thermal enhancement ratios

Tissue and endpoint	Treatment, heating time 1 h	X-ray dose (Gy)	TER
Cartilage 50% stunting	X rays alone	12.90	1.00
	41° before X rays	12.50	1.03
	42° before X rays	9.15	1.41
	43° before X rays	8.10	1.59
Skin Peak reaction at level of 4.0	X rays alone	21.75 (22.00)	1.00
	41°C after X rays	17.25 (18.00)	1.26 (1.22)
	42°C after X rays	15.25 (15.50)	1.43 (1.42)
(average reaction of 2.0)	43°C after X rays	12.75 (14.00)	1.71 (1.57)
Intestine LD/50, 5 days	X rays alone	12.80	1.00
	41.3° after X rays	12.00	1.07
	41.8° after X rays	10.80	1.19
	42.1° after X rays	8.20	1.56

TABLE II

Skin scoring system for mouse ears

0	No visible reaction
1.0	Definite erythema
2.0	Severe erythema
3.0	First sign of breakdown
4.0	Moist desquamation over less than half the outer surface of the pinna, usually covered by crust
5.0	Crust over more than half the outer surface.
6.0	Crust over all the outer surface.

For breakdown of the inner surface the following scores are added:

1.0	Crust over less than half the inner surface.
2.0	Crust over more than half the inner surface.
3.0	Crust over all the inner surface.

Differences in reaction amounting to ±0.33 in score may be resolved. For dry desquamation 0.5 is added. The maximum skin score is 9.0.

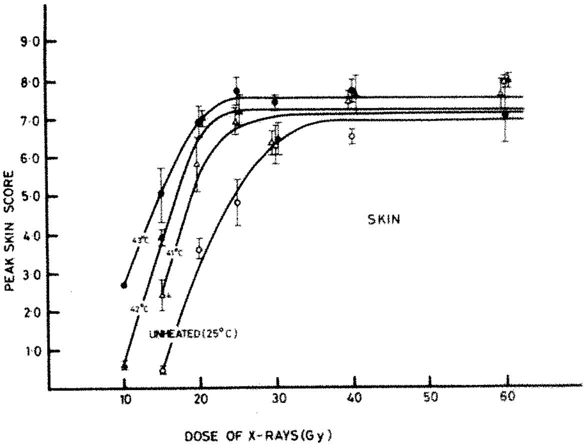

Fig. 2.

Dose response curves for damage to the skin of the ears of mice which had been heated to various temperatures for one hour immediately after irradiation. The response used was the maximum skin reaction.

Table II, in which it is seen that scores of up to nine are possible.

Irradiation alone caused no visible reaction during the first ten days, after which time typical erythema and desquamation developed. Heating at 41°, 42° or 43°C after irradiation was followed by a reddening of the pinna which faded during the first few days. This response was comparable with that due to heating alone. The erythema and desquamation during 10 to 60 days were qualitatively the same as those observed after irradiation alone. Heat alone (up to 43°C for one hour) caused no visible effect during this time.

The magnitude of the response was expressed either as the maximum score or as the area below the response time curve between ten and 50 days post-irradiation. Dose effect curves for the peak reactions are given in Fig. 2 and thermal enhancement ratios for both peak and average reactions are given in Table I.

Intestine

Radiation alone will cause death in mice at four or five days due to damage to the intestine (Quastler, 1956). This may be achieved by whole-body or localized treatment. Heating and irradiation of the abdomen only was used in an investigation of the combined effects of irradiation followed by hyperthermia. Ten to 12 week old female CFLP mice were used with 12 to 18 mice in each group.

For irradiation, the lower body was treated up to the xiphisternum but excluding the legs. For hyperthermia, the lower body of each mouse up to the xiphisternum was immersed in the water bath. Transference between the jig for irradiation to that for heating took approximately three minutes. The increase in temperature, as measured by a thermocouple in the intraperitoneal cavity, was exponential, reaching an equilibrium temperature which was 0.2–0.4°C above the temperature of the water bath six to ten minutes after immersion. The temperatures shown in Fig. 3 are the best estimates of those

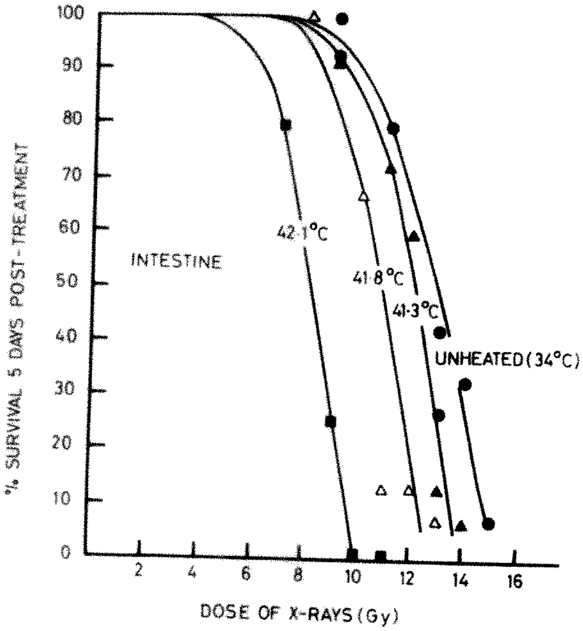

Fig. 3.

Dose response curves for damage to the mouse intestine which had been heated to various temperatures for one hour immediately after irradiation. Only the lower body was heated. The response used was the fraction of animals surviving at five days after treatment, excluding any that died immediately as a direct result of heating.

in the intestine, and the 60 min heating times were taken from the time when the intraperitoneal temperature had reached a steady state. Tolerance of the mice to heat treatment decreased as the intraperitoneal temperature was increased above 41.3°C. Up to 41.8°C, immediate survival was increased by tail vein injection of 0.5 ml of glucose-saline (5%–0.9%), given after heating. Above 41.8°C the injection had no beneficial effect. Death of 50% of the animals occurred within six hours after heating to 42.3°C for 60 min, the highest temperature used in these experiments. Only 10% of mice were able to withstand 42·3°C intraperitoneal temperature for 60 min, an unacceptably high loss.

The hyperthermic treatments alone did not cause death due to mucosal damage. Any mice which died immediately after heating were excluded from the experiment. Apart from these animals, death following irradiation plus heating had a similar time course to that following irradiation alone, and histological sections of small intestine taken three, four or five days after treatment were similar for the two types of treatment. This qualitative similarity enabled a comparison of the two treatments to be made and thermal enhancement ratios were calculated from dose-effect curves using 50% survival at five days post-treatment as the reference level (Table I).

Discussion

The aim of this investigation was an attempt to correlate some effects of combined heat and X rays on tissues in order to establish general patterns of response. Such an analysis is necessary if the methods are to be used clinically to the best advantage and with safety. There are many possible variables, such as temperature, length of heating, dose of radiation, the order of the two modalities and the time interval between them. We have limited this analysis to a constant heating time of one hour and heat given either immediately before or after irradiation. There seems to be little agreement as to which of these is the more effective. Robinson *et al.* (1972 and 1974b) have heated both the C_3H mouse carcinoma and normal skin for one hour plus irradiation. They found, in both systems, no difference in effectiveness between heating immediately before or after irradiation. Similar results were found by Overgaard and Overgaard (1972) using a mouse mammary carcinoma, by Hahn *et al.* (1974) using the Ridgway osteogenic sarcoma, by Crile (1963) using tumours and foot necrosis and by Stewart (1977) using skin reactions in the feet of mice. We did find, with cartilage, that heat was more effective if given first although our result was only for 43°C and 10 Gy of X rays. Thrall *et al.* (1975) also found that heating was more effective if given first to skin, but the reverse was true for tumours in their experiments and also in those of Alfieri *et al.* (1975). Also for experiments *in vitro* there is no general agreement on this point. Therefore, for this first attempt at such an analysis, heating either immediately before or after irradiation is considered. The results are shown in Fig. 4 in which the thermal enhancement ratio is plotted as a function of temperature. Data on skin from Robinson *et al.* (1974b), and Stewart (1977) are included. It is seen that the results for the normal tissues are not widely different from one another and form a consistent pattern of increasing TER with increasing temperature up to a value of about 1.8 for 43°C heating for one hour.

For tumours, the only data which are available for similar analysis for comparison with the normal tissues are those from Robinson *et al.* (1972) and Overgaard and Overgaard (1972) (Fig. 4). These latter authors heated with diathermy which is more difficult to control than heating with hot water as used in all the results discussed previously, and also temperature measurements in an electro-magnetic field are difficult to make and subject to error. In

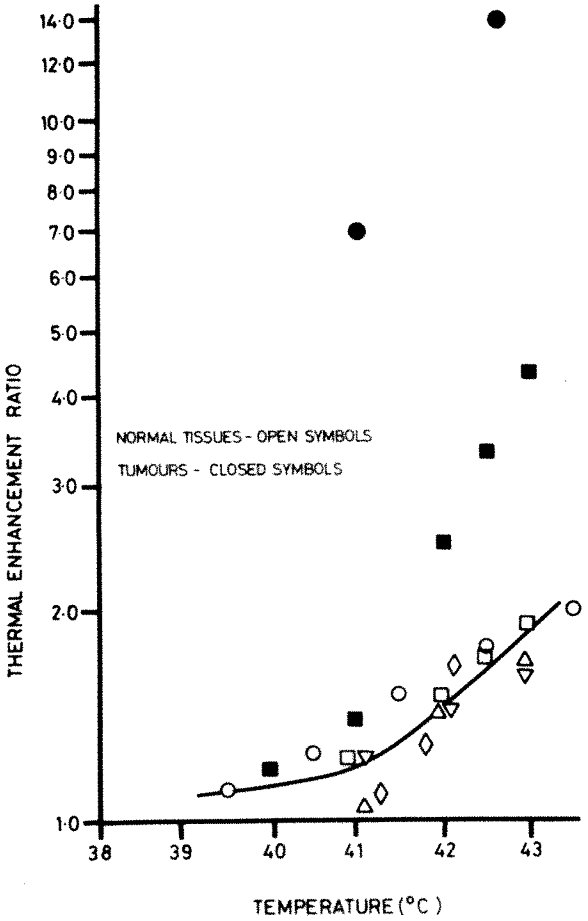

FIG. 4.

Thermal enhancement ratio as a function of heating for one hour to various temperatures. Open symbols represent normal tissues and closed symbols represent tumours: ◇ mouse intestine; ▽ mouse skin; △ rat cartilage; ○ mouse skin from Stewart, 1976; □ mouse skin from Robinson *et al.*, 1974b; ■ mouse tumours from Robinson *et al.*, 1972; ● mouse tumours from Overgaard and Overgaard, 1972.

addition, extraction of thermal enhancement ratios from Overgaard and Overgaard (1972) required some extrapolation, so it must be admitted that these particular results are subject to considerable uncertainty. Even so, the TER values were much greater than for the normal tissues, and Overgaard and Overgaard (1972) did not observe a great deal of damage to normal tissues in their experiments.

Other results on tumours are also worthy of mention although they do not fit into the present scheme of analysis. Thrall *et al.* (1975) compared the response of the C3H mouse mammary adenocarcinoma with that of the skin of the mouse leg. Heating was for 15 min at 44.5°C. They did find a variation in response between heating before or after giving X rays, as mentioned above, and it differed from tumour to normal tissue such that heating after irradiation was relatively more effective in tumour compared to skin than heating first. However, it was found in these experiments that X rays alone generally produced more damage to tumour relative to skin than X rays combined with heat in any configuration. Suit (1977) has made a comparison of a similar tumour and normal tissue, heated for one hour but with heating and irradiation separated by one hour. He also found no advantage in the use of heat, but it is known that the combined effect is reduced as the interval between the two modalities is increased (Thrall *et al.*, 1975; Stewart, 1977; Myers and Field, 1976).

CONCLUSIONS

1. The thermal enhancement ratios for several normal tissues as a function of temperature (heating for one hour either immediately before or after irradiation) do not show a wide variation and give some indication as to safe doses of X rays which may be given combined with one hour's heating.

2. There seems to be an advantage in using heat as well as X rays with some tumours but not with others.

3. Further work is needed to investigate fully the various parameters such as the temporal relationships between heat and X rays and also whether tumours generally have a higher thermal enhancement ratio than normal tissues, which is the requirement for a therapeutic gain.

ACKNOWLEDGMENTS

It is with pleasure that we thank Mrs. Ann Silvester who was responsible for the dosimetry, Mr. Randall Ahier for technical assistance and our many colleagues for helpful discussion. We are particularly grateful to Miss F. Stewart both for advice and for allowing us to quote her results prior to their publication.

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Book review

Radiology of haemophilic arthropathies. By Jenö Forrai, pp. 135, 1976 (Akadémiai Kiadós, Budapest), £4·66.

This monograph consists of 27 pages of text and six pages of references, followed by 88 pages of illustrations.

The text gives a reasonable description of haemophilia with some of its clinical aspects, a description of pathology and radiological appearances, and this description is full and complete. In addition, certain aspects of differential diagnosis are discussed, together with a description of certain aspects of the repair of bone and joint lesions. Some of the English is quaint; "coagulopathy" is not a word which occurs frequently in everyday English.

The bibliography is full and complete up to and including 1973, and certainly gives opportunity for further study of the literature.

The illustrations are positive reproductions of mixed quality, which nowadays are not common in radiological books in the English language. Most readers now prefer negative reproductions.

All in all, this commendable review of a not very common condition is unlikely to appeal to British readers other than to the dedicated worker in the field of haemophilia.

J. H. Middlemiss.

1977, *British Journal of Radiology*, *50*, 135–138

Technical notes

An electronic patient-contouring device*

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The ever-increasing use of computers and more sophisticated methods for obtaining accurate dose distributions has led to the development of methods for obtaining patient contours that are more accurate, faster and convenient than the older schemes that employ plaster bandages or solder wire. Alternative methods that have appeared in recent years include pantographic devices (Krasov and Astrakhan, 1966), electro-optical instruments mounted on treatment simulators (Lillicrap and Milan, 1975), and electro-mechanical contour devices that convert the geometrical coordinates of a movable stylus to electrical signals that are displayed by an X–Y recorder or entered directly into a computer (Simpson *et al.*, 1975; Setala, 1965). In addition, the position transducer that is part of all B-mode ultrasonic scanners is fairly widely used (Smith and Holm, 1970) and the recent introduction of computerized tomography promises to provide not only the patient's contour but internal organ structure as well.

Although we approached the problem of developing a computer-compatible method of obtaining patient contours several years ago, it was only recently that we switched from using plaster bandage to an electronic patient contour device. Our approach was similar to that of Simpson *et al.* (1975). However, as our plans required that the contour device be integral with our treatment simulator, and also as our treatment planning is done on a mini-computer, the final product is quite different.

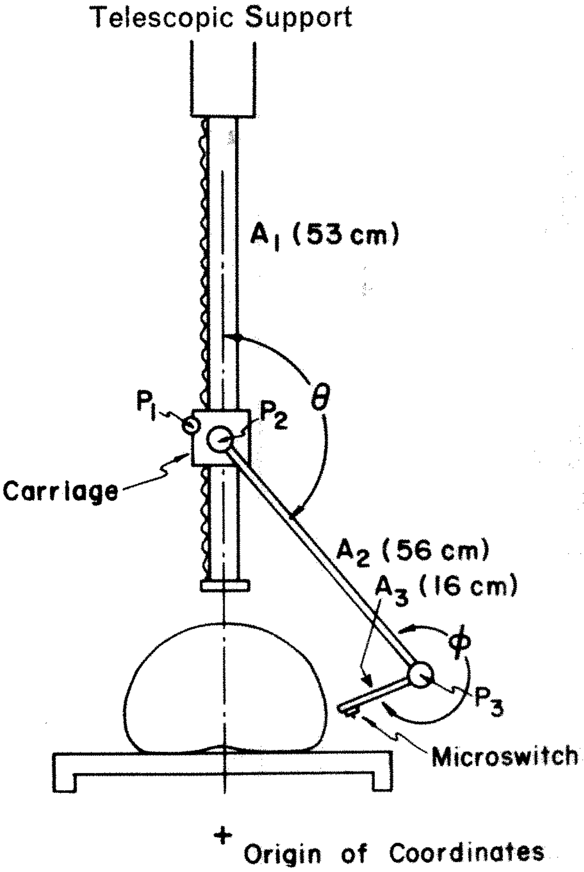

FIG. 1.

A schematic representation of the patient-contouring device. P_1, P_2 and P_3 are potentiometers that measure the vertical height of the carriage, the angle θ and the angle ϕ respectively.

ELECTRO-MECHANICAL DESIGN

The basic geometry and locations of potentiometers on the patient-contouring device are shown in Fig. 1. A small carriage, which carries potentiometers P_1 and P_2, moves vertically on a rigid arm, A_1. A five-turn potentiometer, P_1, is driven by a rack-and-pinion, and its signal is a measure of the vertical height of the carriage. A precision one-turn potentiometer P_2 supports arm A_2, and its signal is a measure of the angle θ. A second one-turn potentiometer P_3, mounted on A_2 and supporting A_3, is used to measure the angle ϕ. The contouring device, as depicted, has been adequate for the largest patients treated in our department.

The triple-armed design of the contour device was selected to permit information gathering from the

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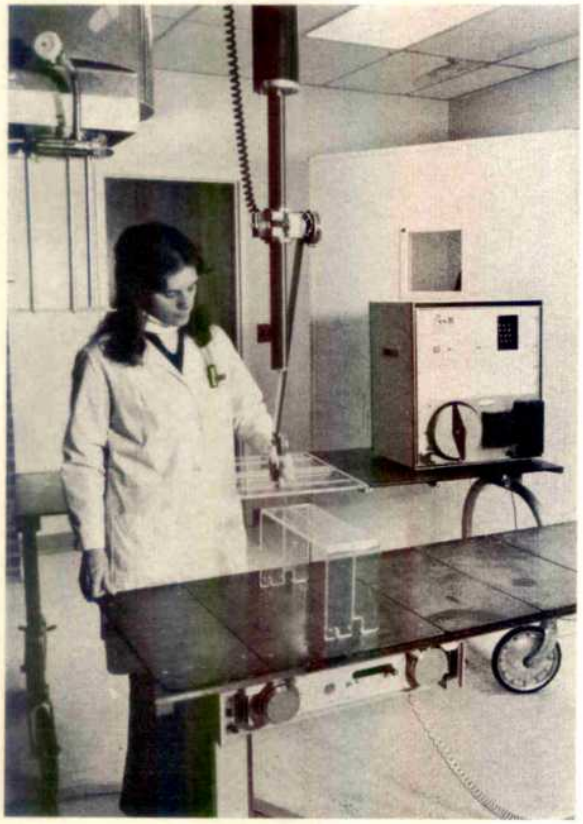

Fig. 2.

The complete patient-contouring device and electronics cabinet. The Lucite test jig is shown in place on the simulator couch.

point at which the patient contacts the stretcher on one side to an equivalent point on the opposite side, with a minimum number of interruptions. In addition, the probe-arm A_3 may be maintained nearly perpendicular to the surface at all locations. This latter consideration is most important when contouring complex surfaces such as in the region of the head and neck.

The contouring device, shown in Fig. 2, is ceiling-mounted and centred over a Varian Clinac-6 treatment stretcher which is used in conjunction with an AECL treatment simulator. The plane of rotation of the simulator is approximately 50 cm from the contouring plane illustrated in Fig. 1. A single, longitudinal shift of the stretcher moves the patient from the simulator X-ray beam to the contouring device. This arrangement allows the contour device to play an integral role in the treatment planning procedure as the location of simulator port films may be entered directly on the patient's contour without any change in the patient's position. When not in use, the contouring device telescopes up toward the ceiling so as to be out of the way.

Algorithm and Data Collection

The signals from the three potentiometers, P_1, P_2 and P_3 are used to establish the cartesian coordinates of the tip of the arm A_3 which contacts the patient. The x and y coordinates are obtained from the trigonometric relationships

$$x = A_2 \sin \theta + A_3 \sin (\theta + \phi - \pi)$$

and

$$y = A_1 + A_2 \cos \theta + A_3 \cos (\theta + \phi - \pi)$$

where A_1 is the height of the carriage above its lowest position (given by P_1). The origin of this coordinate system is on the axis of the arm A_1 and at a point $(A_2 + A_3)$ cm below the lowest position of the carriage.

Each of the potentiometers is biased by a potential of +10 V d.c., and P_2 and P_3 are mechanically adjusted until their signal potentials are 5 V for $\theta = \pi$ and $\phi = \pi$. Over its 53 cm of travel, potentiometer P_1 (0.15% linear) makes 4.5 turns, and only its linear calibration, V/cm, is critical for consistent performance. The signals from the potentiometers are carried to an electronics cabinet which is also located in the treatment simulator room. The electronics cabinet contains a keyboard switch, power supplies, three sample-and-hold circuits (Analog Devices SHA3), a multiplexer (Siliconix DG133 FET switches), analog to digital converter (Zeltex ZD462) and a paper tape punch. A block diagram of the electronics cabinet is shown in Fig. 3. Having entered patient data (in ASCII format) on the paper tape via the numeric keyboard, the dosimetrist may begin a contour by setting the mode switch to the "data acquisition" position. The tip of arm A_3 is placed against the patient, and a small microswitch mounted on that arm is depressed. First, a data-start word (300_8) is punched onto the paper tape, and then the signals from the three potentiometers are sampled simultaneously at a rate of about four samplings per second. These data are stored in the sample-and-hold circuits with minimum decay in value. Before transmission to the multiplexer and paper-tape punch, each analogue signal is converted into 12-bit digital format. These data are sent to the paper-tape punch as two bytes of six bits each so that each point produces a total of six bytes. Therefore, although the three potentiometers are sampled simultaneously, their signals are processed and punched onto paper tape sequentially in time. This process repeats itself until the microswitch on arm A_3 is released.

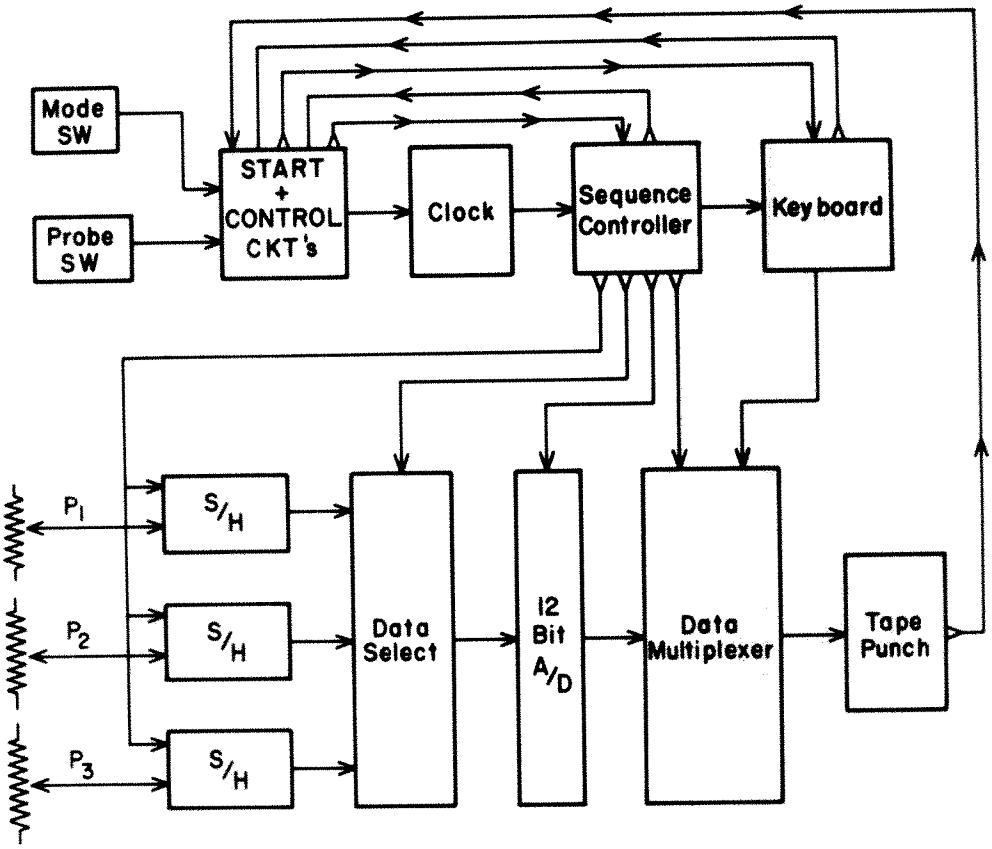

FIG. 3.
Block diagram of the electronics cabinet for the patient-contouring device.

The paper tape produced by the contouring device is read into the PDP-8 computer via a teletype unit in less than 30 seconds. The patient's number is immediately displayed on the screen of the oscilloscope. If a single set of x–y coordinates separated by data-start words are read by the computer, an "x" is displayed at a corresponding location on the scope screen. An "x" is obtained by momentarily depressing the microswitch on the arm A_3, and this is very useful for locating the centres of port films or points of anatomical interest. If more than one set of x–y coordinates are read by the computer, not separated by data-start words, vectors are drawn from point to point producing the patients contour. All the data on the paper tape may be stored on magnetic tape, displayed on the oscilloscope and plotted at full scale by a digital x–y plotter.

APPLICATION

The contouring device requires approximately one minute warm-up time, and is usually turned on before localization films are taken on the simulator. Localization films are taken which indicate the contour level and the centre of the treatment volume. With the patient in the treatment position on the simulator couch, the couch is moved longitudinally so that the contour level, which has been drawn on the patient, is directly under the contouring device. The device is then lowered, locked into place, and the arms checked for freedom of movement around the patient. Next, the simulator couch is raised to a height above the lower limit of the contourer arms and its height checked to ensure that the anterior surface of the patient is below the upper limit of operation.

After the patient has been properly positioned, a length of paper tape leader is obtained by depressing the tape-advance button on the front of the electronics cabinet. With the mode switch in the "keyboard" position, the patient's contour identity number is punched onto the paper tape. The switch is then changed to the "data acquisition" position,

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and the device is now ready to record the contour.

The tip of arm A_3 is placed on the simulator couch to the right and then to the left of the patient. The microswitch on this arm is momentarily depressed in each of these positions, producing two "x" marks. These marks are used to locate the patient contour with reference to the treatment table. The pointer is then placed at the intersection of the treatment table with the patient's surface and the microswitch depressed, beginning the input of contour data. The pointer is then guided along the contour line on the patient's surface. The microswitch can be released at any point and then restarted. After the entire contour has been entered, additional reference marks are made. Mid-line and other anatomical locations which will help to orientate the contour and provide reference points useful for the treatment set-up are routinely entered. Right and left are indicated by "drawing" the appropriate letter in air on either side of the patient. When all essential information has been entered onto the paper tape, the mode switch is placed in the "keyboard" position, and the patient's contour identity number is again punched onto the tape. The second entry of the contour identity number is required by the computer program to terminate the process of data entry.

Confidence checks on the device are performed at weekly intervals with the aid of a Lucite jig shown in Fig. 2. This jig provides a standard contour as well as specific detents which locate identification marks (x's). The plot of the test jig is checked for size, orientation, and accurate location of the identification marks. In the three months that the contouring device has been in operation, the plot of the test jig has never been distorted by more than 2 mm in any one direction.

DISCUSSION

The electronic patient-contouring device is routinely used in our department for contours of patients who are to be treated in the prone or supine positions. Because the device cannot operate in the horizontal plane, contours of patients treated in upright positions continue to be made with plaster of Paris bandage. The device has proved to be of tremendous value when multi-level contours and dose distributions are required. It has the virtues of being fast, accurate, convenient and reliable. However, in order to meet our requirements, it became relatively complex in terms of the task to be performed. It is not everyone's contouring device, and can be justified mainly for larger departments that treat more than 1000 new cases per year, and where comprehensive treatment planning is the rule rather than the exception.

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Urethrography simplified: the drip infusion technique

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There are two radiological methods for examination of the male urethra: retrograde urethrography and micturating cysto-urethrography (MCU). Traditionally these two examinations have been carried out as separate procedures. They are however complementary to each other in the assessment of urethral stricture (de Lacey *et al.*, 1973).

The retrograde study may be performed using a clamp (Brodny, 1941; Knutsson, 1929), a Foley catheter (Hyman and Yulis, 1965; Apap, 1971), or a vacuum apparatus (Becker and Gregoire, 1968; McCallum, 1964). The MCU is frequently requested or booked as a separate procedure, and performed by passing a catheter into the bladder. When a stricture prevents catheterization contrast may be injected either via a supra-pubic puncture, or intravenously with subsequent excretion filling of the bladder (Fumerton and MacEwan, 1970).

It is possible however to perform both retrograde and MCU as one procedure without catheterization of the bladder. This method has several advantages: it eliminates the occasional difficulties which may arise using a clamp in non-circumcised patients or those with phimosis (de Lacey *et al.*, 1973); a urethral stricture which prevents bladder catheterization will not interfere with the procedure in most instances; and fluoroscopy is not essential, which will reduce radiation exposure to patient and radiologist, and allow the procedure to be performed with basic X-ray equipment. In addition this simplified examination is swift, comfortable for the patient and only four films are necessary to demonstrate the entire urethra (Fig. 2). Some radiologists use a viscous contrast medium thickened with carboxy-methyl-cellulose in order to obtain adequate distension of the prostatic urethra on the retrograde study. However, an unthickened water soluble medium yields very satisfactory results when the retrograde and MCU are performed together as one examination (de Lacey *et al.*, 1973). The viscous medium must be injected under pressure and is thus unsuitable for the drip infusion technique.

The procedure is as follows: the patient empties his bladder and is then placed supine on the X-ray table. A control (35×35 cm) film to include the bladder and the whole of the urethra is taken in the 45 deg. right posterior oblique position (Fig. 2A). A No. 8 Foley catheter is connected to a drip infusion set, the contrast medium being water soluble (*e.g.* Urografin 30% or Diodone 25% are suitable). The glans penis is cleansed with an antiseptic, and a small quantity of sterile 2% lignocaine gel introduced into the external urethral meatus as both a lubricant and an anaesthetic. The drip infusion Foley catheter assembly is completely filled with the contrast so as to eliminate air bubbles. The catheter is then introduced into the fossa navicularis and the balloon inflated with water until the patient feels that it is tight. The patient maintains the 45 deg. R.P.O. position and contrast is run into the urethra with the bottle approximately three feet above the table top (Fig. 1). After approximately 20 ml have been introduced an overcouch 35×35 cm film is exposed. The infusion continues whilst this film is being processed, and should it then indicate a necessary alteration in position or radiographic exposure another film is taken. These films adequately distend the urethra as far proximally as the membraneous portion (Fig. 2B). The infusion continues, and is not stopped until the patient expresses an urgent desire to micturate. After catheter removal the patient voids in the same supine oblique position. During micturition a further film is exposed which will show the prostatic and membraneous urethra satisfactorily distended (Fig. 2C). The patient is then told to cease micturition abruptly, at which point a fourth film is taken; the contraction of the external sphincter will usually accentuate the distension of the prostatic urethra. These films are processed and the examination is complete.

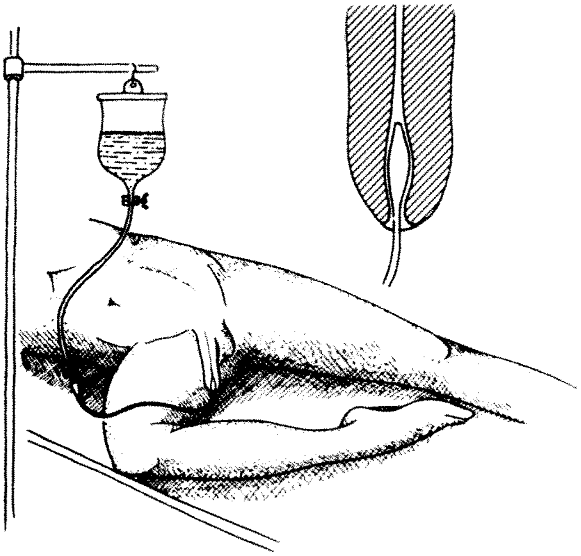

FIG. 1.

The balloon of the Foley catheter is inflated in the fossa navicularis with 2–3 ml of water. The control, retrograde and voiding films are all taken in this position with the overcouch tube.

SUMMARY OF ADVANTAGES OF THE INFUSION URETHROGRAM

(1) Retrograde and MCU can be performed as one simple examination.

(2) Strictures which prevent the passage of a bladder catheter do not interfere with this technique.

(3) The risks attendant on bladder catheterization are avoided.

(4) The low pressure of injection is comfortable for the patient and reduces the risk of peri-urethral extravasation of contrast.

(5) Fluoroscopy is unnecessary and only basic X-ray equipment (even portable apparatus) is all that is required.

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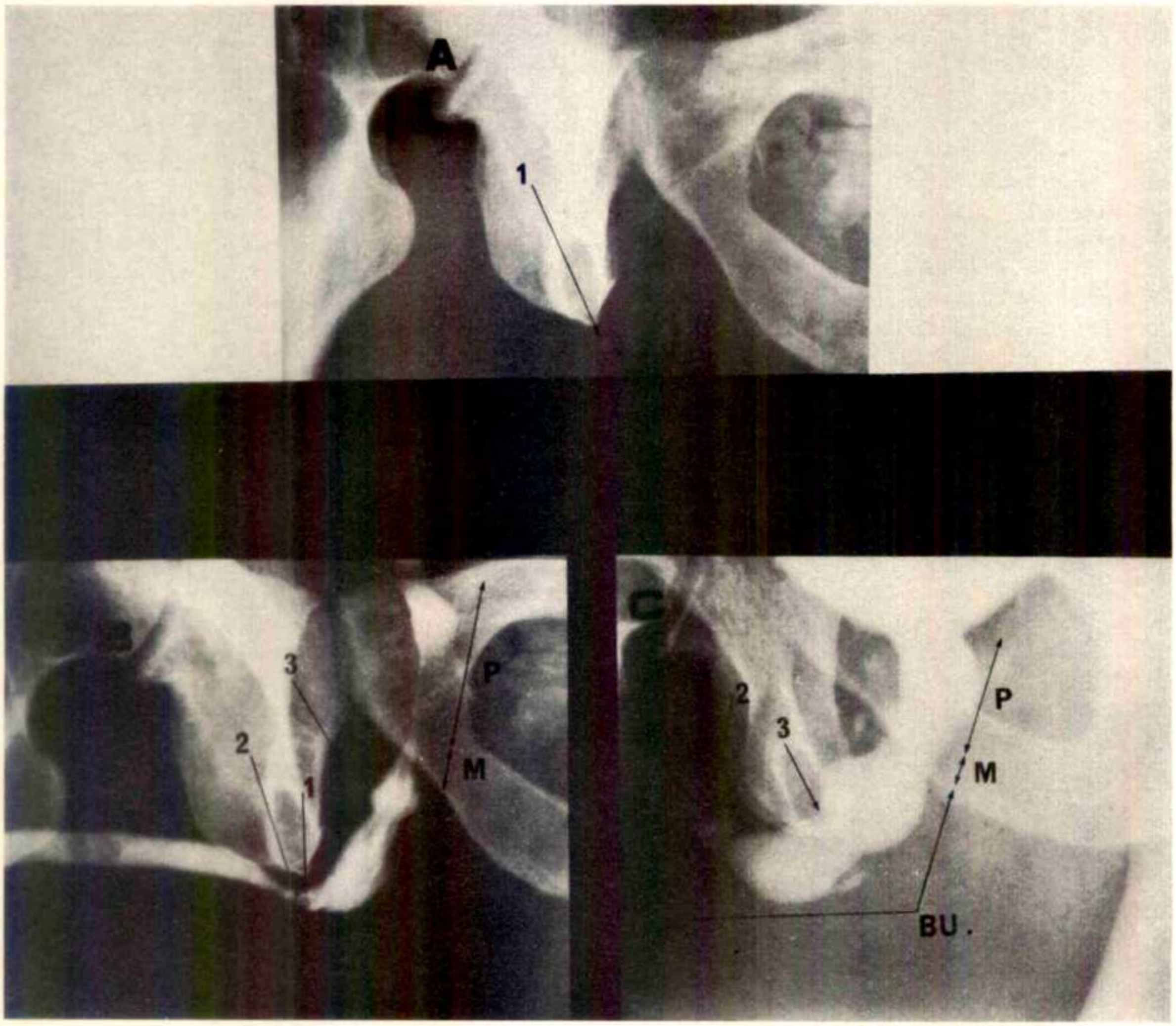

FIG. 2.

Infusion urethrogram (2A control, 2B retrograde, and 2C micturating films).
A small opaque urethral calculus (1) is situated proximal to a narrow stricture (2) in the bulbous urethra (Bu). Another stricture (3) is seen as a slight narrowing in the proximal bulbous urethra and this should not be confused with the membraneous urethra (M). The pendulous urethra (Pen) is best shown on the retrograde film, and the prostatic urethra (P) is shown to be normal only on the micturating film. Two small air bubbles are present in the pendulous urethra and these should have been excluded.

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1977, *British Journal of Radiology*, *50*, 141–142

Case reports

Aberrant renal papilla

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(*Received June, 1976*)

CASE REPORT

A 50-year-old obese black female with lower urinary tract symptoms had a smooth filling defect in the left renal pelvis on intravenous urography (Fig. 1). A left retrograde pyelogram again showed a smooth filling defect in the left pelvis measuring approximately 1.5 to 2 cm in diameter. Because tumour could not be ruled out, the left kidney and renal pelvis were explored. Inside the renal pelvis a dark bluish mass was seen extruding from one of the calyces. This mass was biopsied, and frozen section diagnosis was indeterminate. Therefore the kidney was entirely mobilized, and the renal pedicle clamped with a rubber-shod clamp. A wedge of renal parenchyma overlying the calyceal defect was excised. This allowed a direct view into the renal pelvis, and firm tissue was seen extending from the infundibula. This was dissected down and excised completely. It did not appear neoplastic. Final pathological examination showed benign hypertrophied papilla with no evidence of tumour (Fig. 2).

Post-operatively the patient did well. Follow-up IVP showed reduction in the size of the left kidney consistent with surgery but good function and no complication.

DISCUSSION

Of the many radiolucent filling defects in the renal pelvis and infundibulum, the aberrant renal papilla has been a diagnostic dilemma. This entity was first described by Wolfson and Stowell (1969) and since then three other cases have been reported in the literature (Binder *et al.*, 1972; Feldman *et al.*, 1975). In its typical form, the radiological findings consist of round or oval sharply marginated, lucent filling defects, larger than the usual blood vessel, measuring from 3 to 5 mm (15 mm in our case). They are non-obstructive, and reproducible with essentially unchanged radiographic appearance, except perhaps having a broad base depending upon the projection

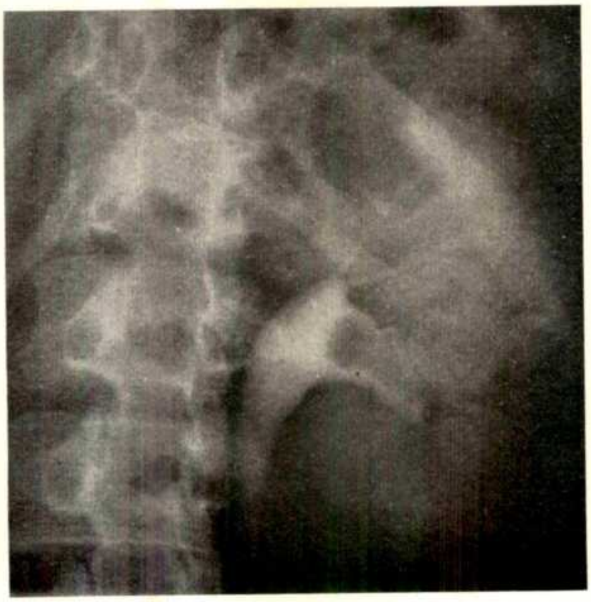

FIG. 1.

Left kidney (oblique view). IVP. 1.5 cm. compression defect involving the pelvis and mid-pole calyx (pre-op).

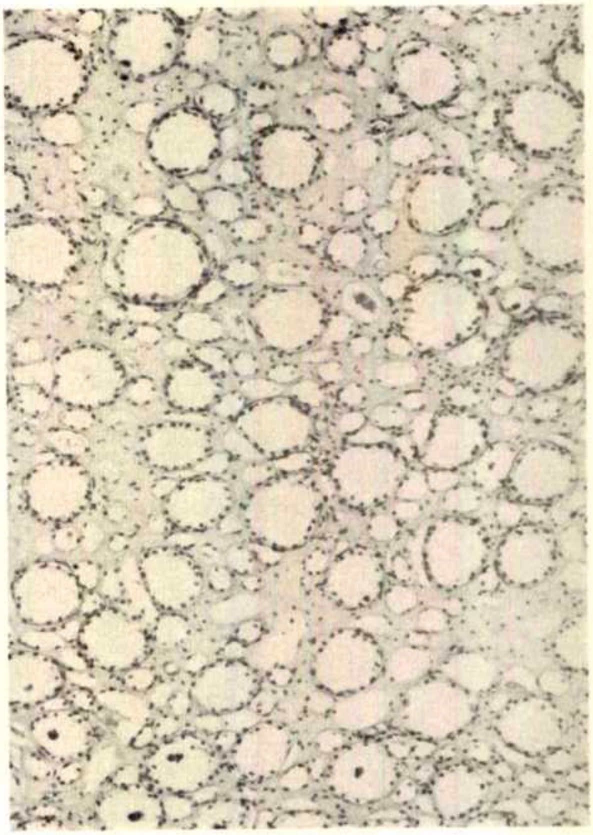

FIG. 2.

Photomicrograph of renal medulla showing normal distal and collecting tubules. There is no evidence of neoplasia.

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and profile of the lesion (Baum and Gillenwater, 1966).

As has been suggested in the past, this represents one end of a spectrum of minor anomalies of calyceal development, and yet presents difficulty in the middle-aged individuals, where tissue biopsy is essential to rule out malignancy. The first three cases were diagnosed only after nephrectomy was carried out. Recognition of this condition has led to a much more conservative approach, *i.e.* excisional biopsy. In our case, wedge resection was carried out.

Repeated urographies with and without compression technique, oblique projections, tomograms, occasional angiography and retrograde pyeloureterogram under fluoroscopy have been carried out. The final diagnosis is usually made by pyelotomy incision and excisional biopsy.

A halo effect surrounding the lucency and its eccentric position in the renal pelvis, in juxtaposition to a major infundibulum, were noted in our case as by Feldman *et al.* (1975).

The number of patients reported so far is small. However, awareness of this condition may lead to discovery of more cases, and alter the management in favour of a more conservative approach of watchful waiting. The lack of symptoms and negative laboratory tests (*e.g.* urinalysis, urine cytology and unchanging pyelogram) will support this diagnosis.

ACKNOWLEDGMENT

The authors wish to thank Shailendra Kumar, M.D. and J. Adolph, M.D. for their invaluable advice.

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Pulmonary lymphangitic carcinomatosis in renal adenocarcinoma

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(*Received May, 1976*)

Lymphatic permeation of the lungs has been described in the terminal phases of carcinoma of the breast, stomach, colon, pancreas, prostate, endometrium, ovary, cervix and bladder (Fraser and Pare, 1970; Heitzman, 1973; Janover and Blennerhasset, 1971). This type of metastatic dissemination from a renal adenocarcinoma has not been previously documented.

CASE REPORT

A 39-year-old black male presented with two weeks' intermittent epigastric and right flank pain. The initial laboratory work-up was non-contributory. The admission chest X ray was normal (Fig. 1A). An excretory urogram and nephrotomogram showed a bulbous right upper pole with calyceal amputation. A selective renal arteriogram with and without epinephrine revealed a minimally vascularized solid mass without evidence of arteriovenous shunting or tumour staining. While undergoing further diagnostic work-up, there was marked progression of the clinical symptoms. Haematuria, anaemia, leucocytosis and persistent fever were then present. A chest radiograph two-and-a-half weeks after admission revealed an increase in interstitial markings with preferential involvement of both perihilar regions and lower lung fields (Fig. 1B). The combination of the chest and urographic findings suggested a diffuse inflammatory process of bacterial or tuberculous origin. A uroepithelial tumour with infiltration of the renal parenchyma was also considered.

The patient underwent right nephrectomy, but there was progressive clinical deterioration and gradually increasing respiratory distress with severe hypoxaemia and hypercarbia. A chest radiograph the day before death disclosed marked progression of the pulmonary lesions, with parenchymal nodularity along with a prominent linear pattern involving both lung fields (Fig. 1C). There was no radiological evidence of mediastinal adenopathy or pleural effusion. Six weeks after admission, the patient died and an autopsy was obtained.

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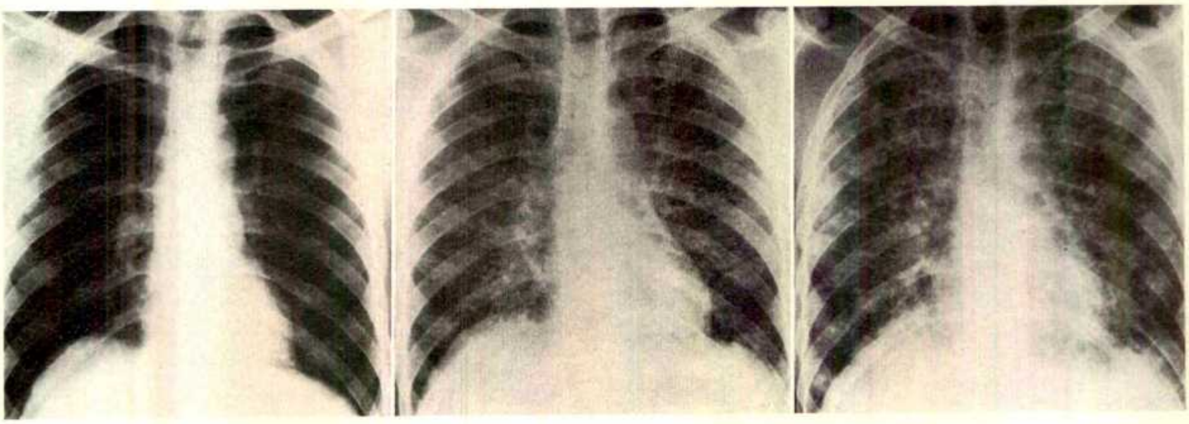

FIG. 1.

Serial chest radiographs demonstrating the progression of interstitial changes between admission and death.

Histologic sections of an indurated right upper pole mass revealed a poorly differentiated renal adenocarcinoma of the tubular-papillary variety. Sections of the lungs demonstrated diffuse tumoural permeation of the lymphatics with desmoplastic reaction of the adjacent connective tissue. Multiple periaortic and mediastinal lymph nodes were involved.

DISCUSSION

Pulmonary metastases from renal adenocarcinoma are regarded as the result of haematogenous spread. They commonly present as either "cannon-ball" lesions, or as miliary nodules in the most aggressive varieties. Instead, diffuse interstitial involvement of the lungs corresponding to tumour invasion of the perivascular and peribronchial lymphatics was seen in this patient.

While pulmonary lymphangitic carcinomatosis of the lungs does occur in aggressive tumours of uroepithelial nature (Janower and Blennerhasset, 1971), to our knowledge this case represents the first reported instance of such metastatic involvement from a tumour of renal cell origin.

Because of unusual clinical and radiological presentation the pulmonary lesions were initially attributed to a generalized infectious process, and their true nature was not suspected until late in the course of the disease.

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Oil cyst of the breast following fat necrosis

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(*Received May, 1976*)

Fat necrosis of the breast is a process of disintegration of fat cells accompanied by a foreign body reaction ending in fibrosis (Harbitz, 1935; Hadfield, 1928). Blunt trauma is considered the main aetiologic factor (Haagensen, 1971) although a history of trauma is not always available (Adair and Munzer, 1947). In some cases surgical trauma has been implicated (Haagensen, 1971; von Hoeffken and Lanyi, 1973).

Pathological examination of areas of fat necrosis not infrequently reveals cystic cavities containing oily or haemorrhagic fluid. However, reports on cystic lesions containing oily material are scarce in the radiological literature. Here will be reported a

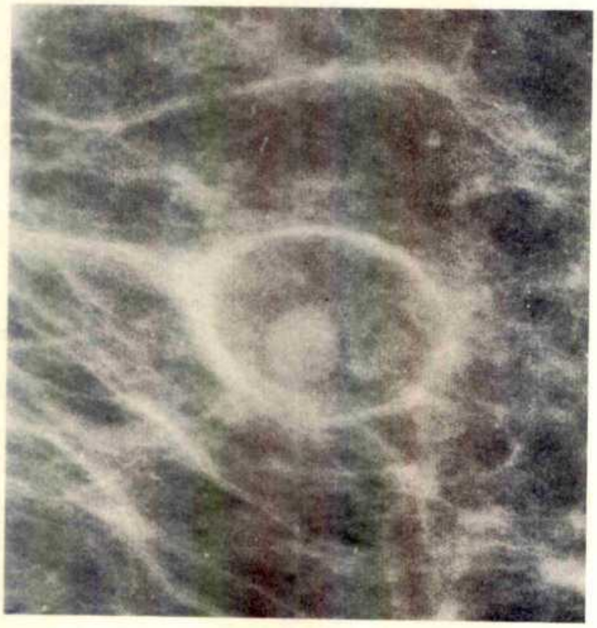

FIG. 1.

Mammography, medio-lateral projection, reveals a round, encapsulated process, with a radiolucency corresponding to fat. It contains a small piece of more radiopaque tissue.

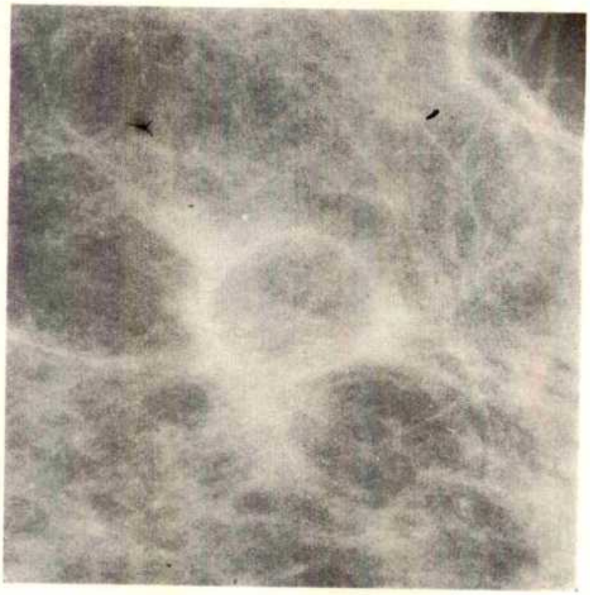

FIG. 3.

Repeat mammography, six months after the first examination and fine needle aspiration. The cyst is somewhat smaller and the dense piece of tissue has disappeared.

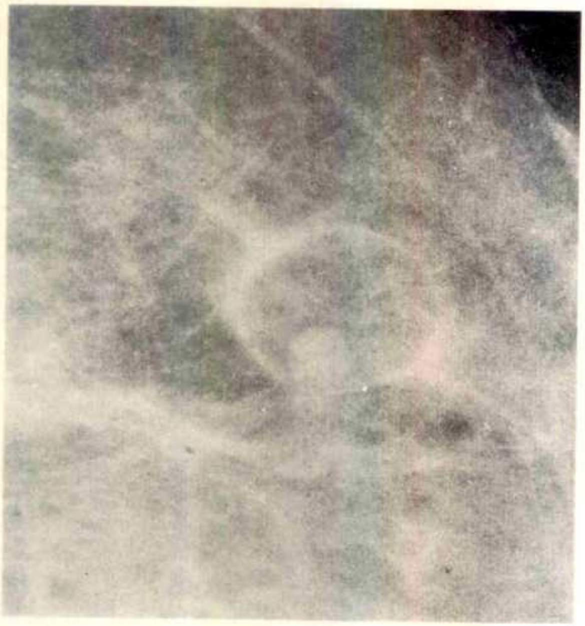

FIG. 2.

By examination in different positions the dense piece of tissue was shown to be situated within the cyst.

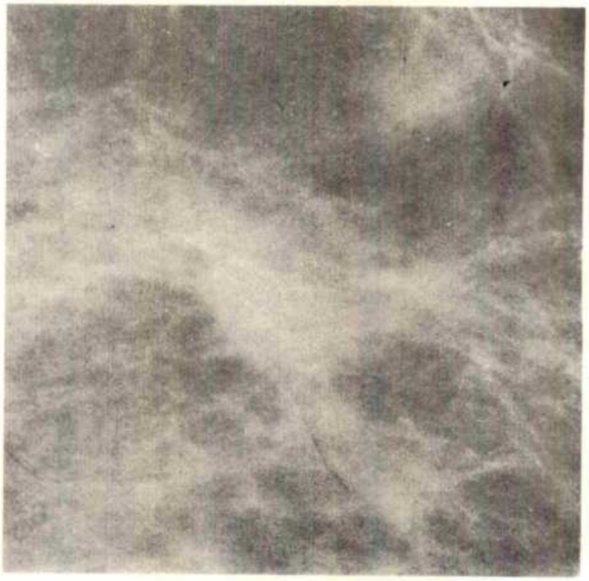

FIG. 4.

After repeat fine needle aspiration the cyst has disappeared, leaving an area of moderate density.

case of an oil cyst revealed at mammography and treated with aspiration of the cyst content which was chemically analyzed.

Case History

The patient, a 60-year-old woman, was operated on because of a benign lesion in the upper, lateral quadrant of the left breast. Post-operatively a 30 × 30 mm hard mass was palpated in the area of operation. The mass, which was interpreted as an haematoma, diminished rather quickly, leaving a small area of induration. Four years later the patient was admitted for mammography because of a 7 × 12 mm tumour beneath the scar in the left breast. The tumour was well delineated but seemed to be fixed to the scar. Mammography revealed a round, well-encapsulated process with a diameter of 20 mm in the upper, outer quadrant of the left breast (Fig. 1). It had the radiolucency of fat tissue, except for a small piece of more radiopaque tissue which was shown to be movable within the cyst (Fig. 2). The radiological diagnosis was oil cyst following fat necrosis. A fine needle aspiration yielded a small amount of fatty material without significant cellular elements. It was not chemically analyzed.

Six months later a repeat examination was done. Clinically and radiographically the cyst had decreased somewhat in size. The dense piece of tissue had disappeared (Fig. 3). Another aspiration was undertaken giving about 4 ml of yellow, oily fluid. Films taken after the aspiration showed the cyst to have disappeared, leaving an area of moderate density (Fig. 4). The lesion was no longer palpable.

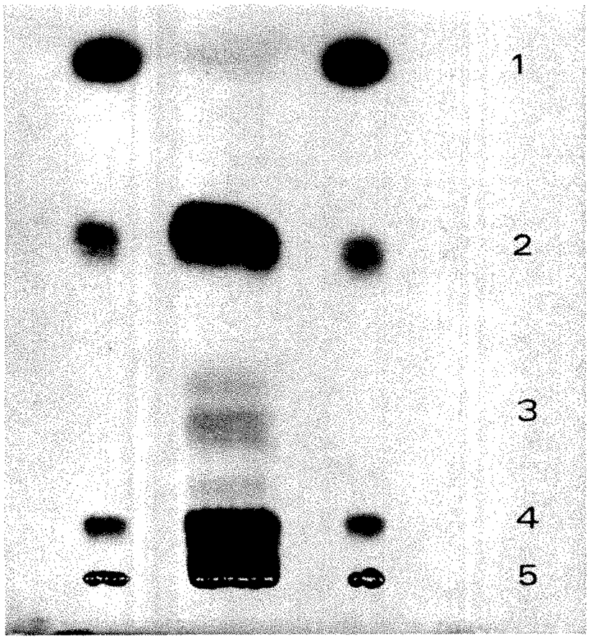

Fig. 5a.

Thin layer chromatogram of oil cyst neutral lipids (middle lane). Human serum neutral lipids (outer two lanes) were run as a reference. The adsorbent was silica gel G (Ag Merck) and the developing solvent was petroleum ether/diethyl ether/acetic acid: 84/15/1 (by volume). The spots were detected by spraying the plate with concentrated sulphuric acid/water 1/1 (by volume) and charring at 200°C: (1) cholesterol ester, (2) triglyceride, (3) free fatty acids, (4) cholesterol and diglycerides, (5) monoglycerides and phospholipids.

Analysis of the cyst fluid showed that it contained about 65% lipid (by weight). The dominating lipid was triglyceride but diglyceride, monoglyceride and fatty acids were also present. If calculated as glyceryl trioleate, glyceride comprised 89.4% of the weight of the lipids. Free and esterified cholesterol amounted to 2% of the lipid weight (calculated as cholesterol). Trace amounts of phospholipid were detected by thin layer chromatography (Fig. 5).

Discussion

Clearly the radiological appearance of fat necrosis depends on the stage in which the lesion is examined. The majority of cases present with an ill-defined mass, often with skin thickening and retraction, thus simulating carcinoma (Coren *et al.*, 1974; Gershon-Cohen, 1970; Minagi and Youker, 1968). Obviously cystic lesions are not a prominent feature in most cases. Cystic, radiolucent, thin-walled cavities as a manifestation of fat necrosis were described by Leborgne (1967) and von Hoeffken and Lanyi (1973). This type of lesion probably represents a late stage of fat necrosis. In the present case the cyst was obviously a sequel of an operation four years earlier.

Calcification of the walls of oil cysts was reported by Leborgne (1967). One of the cases described by Hoeffken and Lanyi (1973) showed a radiopaque intracystic body containing small calcifications. Our

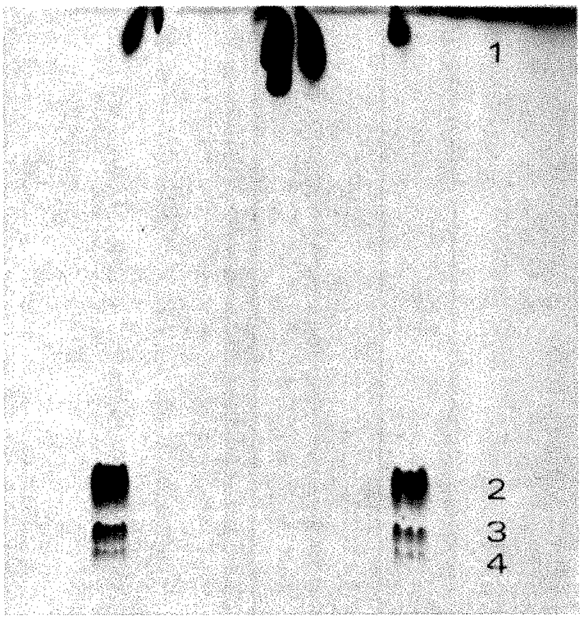

Fig. 5b.

Thin layer chromatogram of oil cyst phospholipids (middle lane). Human serum phospholipids (outer two lanes) were run as a reference. The adsorbent was silica gel H (Ag Merck) and the developing solvent was chloroform/methanol/acetic acid/water: 25/15/4/1 (by volume). The spots were detected as in Fig. 5a: (1) neutral lipids, (2) lecithin, (3) sphingomyelin, (4) lysolecithin.

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case displayed a similar although not calcified piece of tissue on the first examination. The intracystic, relatively radiopaque bodies probably represent not yet liquefied material.

Fat necrosis is frequently mistaken for carcinoma both clinically and radiologically. However, in cases of liquefaction with formation of an oil cyst the X-ray picture is quite typical. The only differential diagnosis that might be considered is an encapsulated lipoma.

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Fever as a complication of low dose irradiation

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Hyperthermia has been well recognized as a frequent component of radiation sickness (Hall, 1973). This syndrome usually follows total body irradiation occurring in lethal accidental exposures. Fever is thought to be an immediate sign of radiation toxicity only after supralethal doses (Lushbaugh, 1969). Cytogenetic effects of irradiation have been extensively reviewed (Bender, 1969). It has been suggested that humans with trisomy 21 have an increased radiosensitivity which may account for their high incidence of granulocytic leukaemia (Sasaki and Tonomura, 1969). Low dose radiotherapy in our patient precipitated marked hyperthermia.

Case History

The patient was a 12-year-old white male admitted for treatment of transplant rejection. In 1970 he developed hypocomplementemic glomerulonephritis for which a renal transplant was preformed (May 1970). In May 1972, because of repeated episodes of rejection, a transplant nephrectomy was performed. In May 1974, a cadaver transplant (B match) was accomplished, but the patient had immediate and progressive rejection. In September 1974, because of declining renal function, he was admitted for treatment. His medications on admission included Azothiprine 35 mg per day and Prednisone 40 mg per day.

Physical examination revealed a chronically ill white male. Vital signs (including temperature) were normal. A palpable non-tender kidney was noted in the left lower quadrant. Also a two component pericardial friction rub was found.

Laboratory evaluation showed Creatinine 4.3 mg%, WBC 3200, Differential: Seg 55, Bands 5, Lymphs 32, Mono 8, Hematocrit 21 vol. %. Urine analysis showed 3+protein, 3–5 WBC/hpf, no RBC's or casts. Total hemolytic complement was repeatedly normal.

Hospital course: initial treatment with four doses of solumedrol (1 gm) every other day failed to control renal function. Therefore low dose pelvic irradiation was begun with 150 rad of γ rays on alternate days. Each course of irradiation was followed by severe prostration and fever in approximately two to four hours (Fig. 1). Cultures of blood, urine, throat and stool failed to reveal any pathogenic organisms. Renal biopsy revealed changes of rejection. No

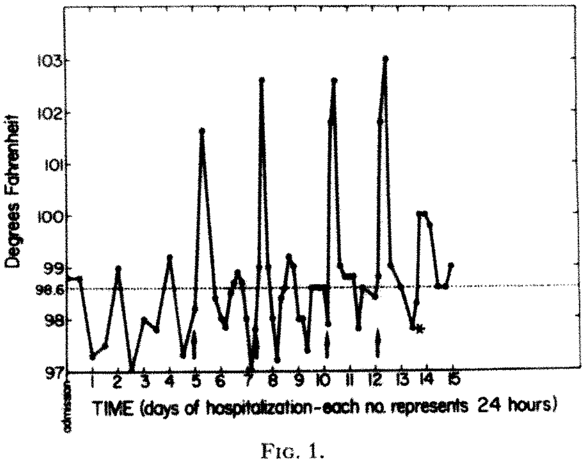

Fig. 1.

Temperature curve (°F) for the patient. The arrows (↑) represent the radiation treatments of 150 rad to the pelvic kidney. The ∗ represents the time of renal biopsy. Marked hyperthermia occurred immediately following radiation.

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acute radiation damage was seen. Chromosomal studies were attempted but an adequate number of cells could not be cultured.

DISCUSSION

This case shows an unusual effect of therapeutic radiation. The more frequent side effects of nausea and vomiting were not present. Errors in dosage cannot explain the fever because the dose was double-checked at the third and fourth irradiations. Marked tissue necrosis was not seen in the renal biopsy and therefore cannot explain the fever. The mechanism of this radiosensitivity might be increased chromosomal breakage leading to cell death. Immunosuppressives and other medications may cause chromosomal breaks. In our patient the long term use of immunosuppressives may have potentiated radiosensitivity, thereby causing cell death evident by fever. Unfortunately the lymphocytes could not be cultivated due to chronic azotemia and dialysis. Our patient represents a previously unreported manifestation of low dose irradiation.

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Selective phalangeal tuft fractures in a guitar player

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(*Received June, 1976 and in revised form August, 1976*)

A case of phalangeal tuft fractures involving the left thumb and index finger and the right middle finger is presented. The interesting radiographic pattern helped in the identification of the aetiology of injury as that of mechanical stress to the guitar-playing fingers. It is probable that the young age at which the child was introduced to the guitar and his juvenile rheumatoid arthritis may have increased his susceptibility to these injuries.

CASE PRESENTATION

An eight-year-old Puerto Rican male was first admitted to Greenpoint Hospital in November, 1974 with juvenile rheumatoid arthritis. The patient had not been previously treated with steroid. There was no family history of acro-osteolysis.

Radiographic studies of both hands showed periarticular soft tissue swelling consistent with juvenile rheumatoid arthritis. In addition, there were phalangeal tuft fractures involving the left thumb and index finger and the right middle finger (Fig. 1). A subsequent skeletal survey showed no other site of injury. The child has been an avid guitar player since the age of five.

A follow-up X ray of both hands on September 9, 1975, again showed fractures of the tufts of the left thumb and right middle finger, the fracture of the left index finger had healed.

DISCUSSION

This case demonstrates selective phalangeal tuft fractures in the hands of a guitar-playing child. Clinical investigation failed to elicit any history of injury or child abuse. Knowledge that the child had enthusiastically played the guitar for the past three years and the selective location of the fractures indicate that the mechanical stress to the guitar-playing fingers is the aetiology of the findings

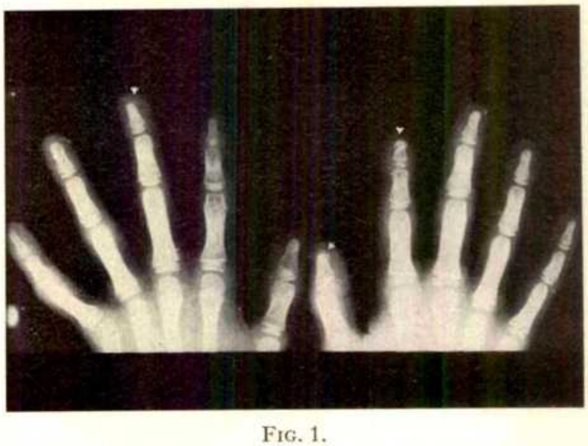

FIG. 1.

Radiographs of both hands showed periarticular swelling consistent with juvenile rheumatoid arthritis. Note tuft fractures of the left thumb and index finger and right middle finger (arrows).

(Zatzkin, 1965). Observation of the patient's playing of his guitar confirmed the fact that mechanical stress is greatest on the three fingers involved. It is probable that the young age at which the child was introduced to the guitar, and his juvenile rheumatoid arthritis, may have increased his susceptibility to these injuries.

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Book reviews

Die Lungentuberkulose im Röntgenbild. By Herbert Blaha, pp. viii + 388 (Berlin, Heidelberg, New York, Springer-Verlag), $159.90.

This monograph in German deals with the radiological appearances in pulmonary tuberculosis. It provides a comprehensive study of the subject with some additional useful clinical, epidemiological and pathological data.

It is not surprising that no new material of any major significance is included in the text; most of the information can be found in textbooks on pulmonary disease. The author has been able to collect most of the data from the literature under one cover and in so doing has provided a very extensive bibliography which is not only of great historical interest, but also brings the reader up-to-date. To the reviewer this part of the book is probably the most valuable contribution. The book is profusely illustrated, but unfortunately the quality of some of the illustrations is not very adequate and it is difficult at times to identify the lesions. This is made even more difficult since the reproductions are positive prints, which are not commonly used in the English literature.

The price of this monograph is prohibitive at $159.90, and for this reason this book will probably only find its way on to the library shelves.

R. E. Steiner.

Extremitätenarteriographie. By W. Wenz and D. Beduhn, pp. x + 158, 1976 (Berlin, Heidelberg, New York, Springer-Verlag), $60.70.

This German contribution to angiography of the extremities, including phlebography and lymphangiography, is a relatively short text covering a very extensive field of radiological knowledge. The authors have tried to give a comprehensive review of both technical and clinical applications of the various methods of investigation. It is inevitable that in a monograph of this type it is impossible to do justice to this undertaking. Most of the material covered can be found in other large publications on this topic, particularly in the English literature, and there is very little information presented which is new and not available elsewhere.

Since the cost of this 160 page monograph is $60.70 it is hard to see how one can recommend it as an important and significant contribution to the topic.

R. E. Steiner.

1977, *British Journal of Radiology*, *50*, 149–150 FEBRUARY 1977

Short communication

Response time constants of two commonly used dose-rate meters

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(*Received May, 1976 and in revised form August, 1976*)

Dose-rate measuring instruments commonly used during radiation protection surveys include ionization chamber types such as the Ekco N596, or the Nuclear Enterprises NE0500. This type of instrument is convenient to use as it is battery operated, portable, and gives a direct meter reading of the dose-rate. A problem can arise however in modern diagnostic X-ray departments where the equipment is normally designed for short exposure times.

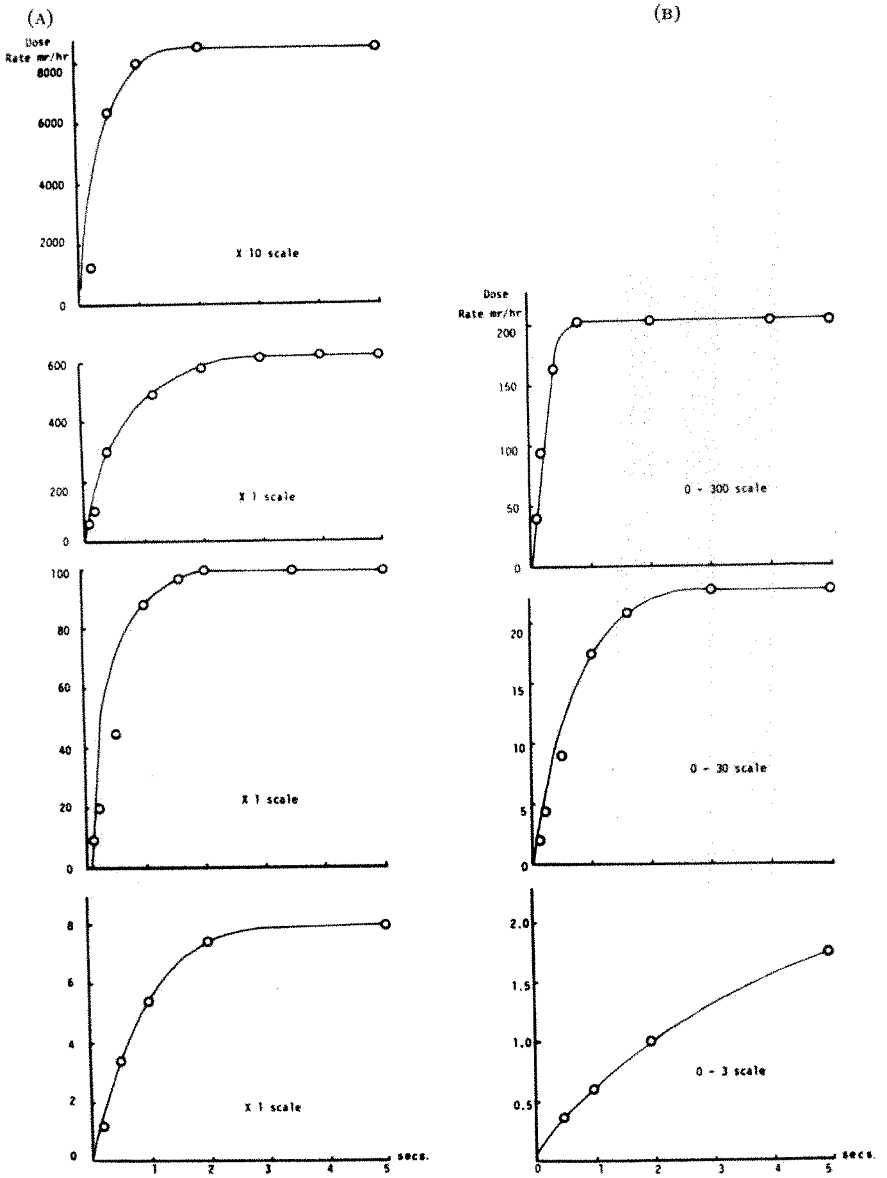

FIG. 1.
(A) Response curves for NE0500.
(B) Response curves for EKCO N596D.

To perform dose-rate measurements with the X-ray unit operating at its maximum rated tube current and kilovoltage the maximum exposure times possible without overloading are frequently so short that allowance must be made for the response times of the above measuring instruments. Details of response times are normally inadequately specified or not given in the manufacturer's operating instructions. As it may not be generally recognized how large the required correction factors can be, and how they can vary with dose-rate range, some details of measurements using instruments of the above type are presented.

METHOD AND RESULTS

A mobile X-ray unit operated at 70 kV was used to make exposures from 0.1 up to 5 seconds. The dose-rate meters were placed at different distances to give dose-rates covering the meter ranges. The observed dose-rates, D_0 for various exposure times are shown in Fig. 1a and b.

The plateau values of these curves give the true dose-rate D_T. If log (D_T—D_0) is plotted against the exposure time T the time constant of the instruments at various dose-rate levels can be readily obtained and are shown in Table I.

CONCLUSIONS

When using this type of instrument to measure dose-rates in the vicinity of a diagnostic X-ray unit it is clearly desirable to lengthen the exposure time as much as possible even if the tube current has to be reduced and the resultant measured dose-rate increased accordingly. Even when this is done, and on the occasions when it is not desirable to reduce the mA, the exposure times may still not be sufficiently lengthy to permit an accurate dose-rate measurement without applying a correction for the time constant of the dose-rate meter.

It is suggested that this easily ascertained and useful information should be incorporated in manufacturers' brochures.

TABLE I

EXPERIMENTALLY DETERMINED TIME CONSTANTS AT DIFFERENT DOSE RATES FOR THE EKCO N596D AND NUCLEAR ENTERPRISES NE0500 RADIATION DOSEMETERS

NE 0500	Dose-rate (mr/hr)	8	100	620	8500
	Time constant (seconds)	1.3	0.70	0.84	0.45
EKCO N596D	Scale range (mr/h)	0–3	0–30	0–300	
	Time constant (seconds)	3.3	0.87	0.15	

Book review

Mathematical Preparation for the Health Sciences. By Joseph I. Routh, pp. 157, 2nd edn, 1976 (Philadelphia, London, Toronto, W. B. Saunders Co.), £4·75.

This is a book for laboratory technicians. The author states that he "has been convinced of the need for a book that would assist a student in applying his mathematical knowledge to the solution of practical laboratory problems. The shortcomings so frequently observed in a scientific discipline or laboratory are the inability to apply these skills to a practical problem and the failure to recognize as correct or incorrect the answer that is the end result of the student's efforts".

The book goes some way to supplying this need with chapters on concentration of solutions, hydrogen ion concentration and pH, buffers, renal clearance calculations, spectrophotometric calculations and radiologic calculations. This sort of cook-book approach is fine if you can find an example of your particular problem in the appropriate chapter but limits the width of appeal of the book by ignoring the fact that the same sort of calculation can often be applied to problems in several different branches of science and technology. Also the two chapters (one fifth of the book) on logarithms and slide rules are surely superfluous in these days of cheap electronic calculators, and give the book an out-of-date air. The space could have been better utilized by expanding the brief, final chapter on quality control statistics. This is a book of limited usefulness.

C. BOWLT.

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

ANALYSIS OF DOSE, DOSE-RATE AND TREATMENT TIME IN THE PRODUCTION OF INJURIES BY RADIUM TREATMENT FOR CANCER OF THE UTERINE CERVIX

In a recent paper with the above title by Lee *et al.* (1976), it is claimed that dose-rate is a more important parameter in modifying the risk of normal tissue injury in radium therapy than treatment time. However, this conclusion is based on an incorrectly plotted graph and data which is not self-consistent.

In Fig. 2 of that paper, the authors have plotted the ureter cases, numbers 9, 10, 12, 13 and 14 as injuries whereas they list these cases as non-injured in Tables I and II. Also, Case 13 is listed as having injury to the rectum in Tables I and IV but is plotted in Fig. 2 as non-injured. Once these corrections have been made there are the same number of injured and non-injured cases each side of the line given by the goodness of separation technique (Kagan *et al.*, 1973) regardless of whether the data are plotted as a function of time or dose-rate. In counting the points, one must allow for the fact that in Fig. 3, rectum Case 15 has not been plotted and rectum Case 9 and ureter Case 3 have both been plotted as bladder cases.

Furthermore, it may be seen that for Case 11 in Table II, Cases 5, 12 and 15 in Table III and Case 15 in Table IV, the figures for dose, time and dose-rate are not self-consistent. Therefore, a further plot of this data would be meaningless without first determining the correct values.

However, it is not necessary to re-plot Figs. 2 and 3 to show that the relative positions of the points would be the same on both. Since the three parameters involved are interdependent, dose $(D) = \text{time } (T) \times \text{ dose-rate } (R)$, Fig. 3 may be obtained from Fig. 2 by using the transformation $(t, d) \rightarrow (r, d')$, where $r = d/t$ and $d' = d$. Then it can easily be shown that a straight line of the form $D = aT^{b}$ on Fig. 2 would become another straight line of the form $D' = a'R^{b'}$ on Fig. 3, where a and b are constants. From this it follows that the relative positions of the data points on the two graphs cannot change.

The slopes of the two lines on the log-log plots are related by the expression $b' = b/(b-1)$. Thus, the line with a slope of 0·3 drawn by the authors on Fig. 2 would have a slope of −0·4 on Fig. 3, which is what they found.

Therefore, one cannot base any conclusions about the relative importance of time or dose-rate from the data presented in this paper. Perhaps one could conclude that it looks as though the isoeffect curve of Paterson (1963) is still our best guide.

The dose to the organs at risk from external beam treatment raises further doubts about this paper. Although the authors assumed this dose was insignificant as a result of shielding, column 6 of Tables II, III and IV lists doses of several thousands of rad from external treatment to these organs for many cases. In some instances, this dose is greater than that from radium treatment. How is it that Case 2 received no external treatment according to Table 1, yet the ureters, bladder and rectum of that patient each received 4,500 rad from external irradiation according to Tables II, III and IV?

Finally, it need hardly be said that for a paper to be published containing so many gross errors which invalidate all of its conclusions reflects rather poorly on the Editorial Committee of this journal.

Yours, etc.,
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The Editors deeply regret that this paper did not receive the careful attention that should have been given to it. The fact that such errors can occasionally slip through our scrutiny demonstrates the need for thorough refereeing of all papers and shows that the delay this introduces must be accepted.—THE EDITORS.

THE EDITORS—SIR,

ANALYSIS OF DOSE, DOSE-RATE AND TREATMENT TIME IN THE PRODUCTION OF INJURIES BY RADIUM TREATMENT FOR CANCER OF THE UTERINE CERVIX

We are most appreciative of the thorough review by J. E. Saunders (1977) of our recent paper. Many of the errata pointed out by Mr. Saunders are indeed verified by our records. In Tables I–IV, the following changes should be made: in ureter case 11, the treatment time was 105 hours; the dose rate was 50 rad/h. The dose rate for bladder case 5 was 58 rad/h, for case 12, 60 rad/h and for case 15, 58 rad/h. In rectum case 15 the dose rate should be 112 rad/h. The external beam dose for case 2 should be 3500 rad in Table I.

Replotting of Figs. 2 and 3 as shown does not, however, invalidate our conclusion that dose rate is more important than time in analyzing the risk of normal tissue injury. It is true that dose rate and treatment time are not independent variables. Thus, there will be the same number of injured and non-injured points on either side of the separation line, no matter whether the data are plotted on the dose-time or dose – dose rate plane. We do not claim that the Strandqvist separation line in the dose – dose rate plane is a better separation than in the dose–time plane.

Our analytic method attempts to break away from the confines of a single Strandqvist line to define a maximum dose and dose-rate that can be used without excess injury to the normal tissues. We have done so in a corrected version of our Fig. 3 with the drawing of a horizontal line at 4500 rad maximum dose and a vertical line at 60 rad/h maximum dose-rate to define the region of low injury risk. A single Strandqvist line does not separate the injured from the non-injured as adequately as our method.

We expect dose-rate to be more important than time as a modifying factor of dose, on the basis of radiobiological data and clinical experience. Hall (1972) showed rapid decrease in the dose needed to reduce a cell population to 37% of its initial number when the dose-rate was increased from 100 rad/h to 100 rad/min, the dose-rate commonly encountered in brachytherapy. Similarly, chromosome aberrations have been shown by many investigators to increase rapidly with increase in the applied dose-rate (Brewen and Luippold, 1971; Scott *et al.*, 1970 and Mello *et al.*, 1974).

The contribution of external beam dose to the normal tissues undoubtedly complicates our analysis of the brachytherapy technique. The number of patients treated by radium therapy alone for cervical cancer is too few to permit

1977, *British Journal of Radiology*, *50*, 152–153

Correspondence

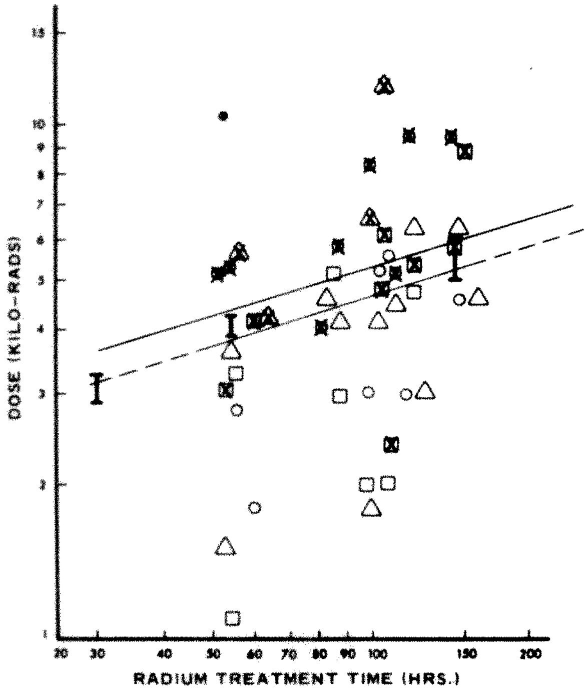

FIG. 2.

Separation of the injured and not injured organs in a Strandqvist plot. The symbol □=bladder, △=rectum, and ○=ureters. A symbol with a ⊗ superimposed on top of it represents injury to the organ.

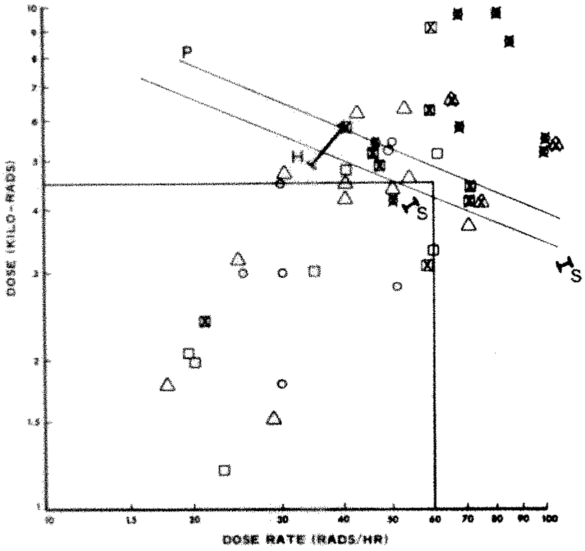

FIG. 3.

Separation of the injured and not injured organs in the dose and dose-rate plot. The symbols □=bladder, △=rectum, ○=ureters. A symbol with a ⊗ superimposed on top of it represents injury to the organ.
P=Paterson's dose – dose-rate curve.
S=Stockholm techniques.
H=Houston techniques.

a meaningful analysis. We therefore have to accept the external beam dose as an uncertainty in our analysis and view our results as preliminary.

However, we are convinced that dose-rate is a more important modifying factor not only because of our data and a large body of radiobiological data, but also because it leads to an important focus on two critical problems in radiotherapy-tumour recurrence and normal tissue injury. In regions of low dose-rate, low dose would be associated with tumour recurrence while in regions of high dose-rate, high dose would be associated with normal tissue injury. Radiation therapists should therefore pay increased attention to these regions.

We hope that the result of our study will encourage other investigators to employ similar analytical techniques rather than rely on the sole use of Strandqvist separation lines.

Yours, etc.,
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THE EDITOR—SIR,

APPLICATION OF A RADIOTHERAPY SIMULATOR FOR IMAGING OF BODY CROSS SECTIONS

A map of cross-sectional tissue structure and associated linear attenuation coefficients within the body contour makes possible accurate treatment planning for radiation therapy. The high cost of transverse body section computerized tomographic (CT) scanners now available commercially will probably limit their application for this purpose to comparatively few departments of radiotherapy. However, the ability to obtain cross-sectional information using a modified radiotherapy simulator puts the possibility of CT aided treatment planning within reach of a far wider group of hospitals. The advantages of adapting commonly available equipment have been pointed out by Smith *et al.* (1976) and we have been exploiting them for some time. They are well summarized by Harrison and Farmer (1976) in the September issue of this Journal.

We have successfully computed the distribution of tissue within a two-dimensional slice of a chest phantom using data recorded on film attached to a treatment simulator. The 100 kV X-ray beam is a narrow fan spanning the phantom and defining the section to be reconstructed from linear shadowgraphs. By racking a grid-screen film cassette within a lead-lined guideframe, exposing the film in strips, whilst simultaneously rotating the phantom, a complete set of transmission projection data corresponding to rotations in equal angular increments was recorded on a single film.

Digital projection data were obtained by measuring the density at 2 mm intervals using a Joyce Loebel microdensitometer. The two-dimensional picture was reconstructed by the divergent data form of the convolution and back projection algorithm within the SNARK 75 computer reconstruction package (Herman *et al.*, 1975) implemented on a CDC 6600 machine at the University of London Computer Centre. Reconstruction and display of a 65 × 65 matrix representation of the two-dimensional distribution from 36 linear projections typically takes one minute. The reconstruction can be displayed on a line printer and as a microfilm greyscale picture. The latter is visually pleasing but turnover time is longer than for the former which is adequate for planning purposes. The phantom reconstructed in Fig. 1 contains lung equivalent material, four ribs, sternum and spine embedded in tissue equivalent wax. All the anatomical features are faithfully reconstructed, in particular the lung outline is determined to ±0.5 cm. An added bonus is the simultaneous generation of the body outline.

The relationship between the resolution attainable, the size of the reconstructed object and the number of contributing projections has been extensively discussed in the literature. In particular Klug and Crowther (1972) and Gilbert (1972) proved that to resolve a spatial frequency R_1 within an object of radius a, $2\pi aR$, views are required. Goitein (1972) independently showed that to resolve $n \times n$ picture elements $4\pi n^2$ measurements must be made equally distributed among $2\pi n$ equally spaced views. The sampling criteria are quite independent of the reconstruction algorithm employed and apply for reconstructing general objects about which no *a priori* information is available. It is clearly evident from the success of our reconstructions that less stringent criteria can be adopted when the objective is limited to identifying anatomical edge structure within an otherwise uniform section. For this situation Ramachandran and Lakshminarayanan (1971) arrive at the empirical sampling condition that $2\pi r/d$ views are required for picture resolution r and detector sampling interval d. In agreement we find that the anatomical structure is still observable when only 18 or 12 projections contribute to the reconstruction. With a reduced number of views the picture elements are no longer independent and the tangential streaking, only just apparent with 36 views, is more pronounced (see *e.g.* Pelc *et al.* (1976) and Barnes (1976)). In interpreting any reconstruction one must be aware of sampling criteria and not attempt to extract more information than is contained in the contributing data.

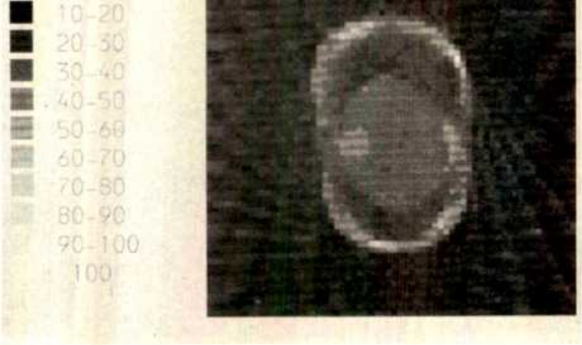

FIG. 1.

65 × 65 bin reconstruction of a chest phantom composed of three tissues, displayed with 11 levels of grey. One bin corresponds to 5 mm.

We are conscious of many potential difficulties. In choosing to operate at 100 kV we hope to minimize spectral effects and the effects of beam hardening. The dynamic range of film detector is not wide enough for the system to record linearly all absorption line integrals. However, by carefully choosing the exposure it is possible to exploit the film non-linearity at low density to suppress the bone-tissue interfaces and enhance tissue-lung interfaces in reconstruction. Picture degradation by scattered X rays has been minimized using a grid and small beam width.

In conclusion it appears to be possible to compromise between the conflicting requirements of minimum patient dose and handling time and the desirability of recording a large number of projection shadowgraphs provided the limited objective is to depict structural boundaries. Encouraged by the phantom reconstructions obtained we are currently working towards an *in vivo* study.

We wish to thank Dr. R. P. Parker for most helpful discussions.

Yours etc.,

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1977, *British Journal of Radiology*, *50*, 154

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THE EDITOR—SIR,

LATE EFFECTS OF X IRRADIATION IN PATIENTS TREATED FOR METROPATHIA HAEMORRHAGICA

Mr. Smith and Professor Doll in their recent interesting paper (Smith and Doll, 1976) suggest that low dose ovarian irradiation (X-ray artificial menopause, XRAM) in the treatment of metropathia haemorrhagica produces "an effect on ovarian function, in relation to the development of breast cancer, which is different from the corresponding effect of a natural menopause, or of a surgically induced menopause".

I suggest that one possible explanation for this continued protective effect against breast cancer by XRAM in patients over the age of 50 years is the presence in the ovary of radio-resistant cells secreting an androgenic hormone. The fall in circulating oestradiol during the months following XRAM leads to increased gonadotrophin secretion by the pituitary; this may stimulate cellular elements in the ovary which, unlike the follicles, have been unaffected by the usual XRAM dose of about 500 rad.

In addition to oestrogenic substances, the ovaries and adrenals both secrete androstenedione, some of which is converted into testosterone (Fox and Langley, 1976). The "interstitial tissue" produces most of the ovarian androgens (androstenedione, dehydroepiandrosterone and testosterone) (Savard, 1968). In the testis the interstitial Leydig cells are the main site of androgen secretion; it is not yet definitely known however which component of the ovary is responsible, although most ovarian Leydig cell tumours are androgenic (Fox and Langley, 1976).

Having said all this, one has to admit that, because the opportunity arises so very rarely to examine the ovaries of a patient fairly recently subjected to XRAM for menorrhagia, there is very little available information about the histological appearance of the interstitial tissue of such ovaries.

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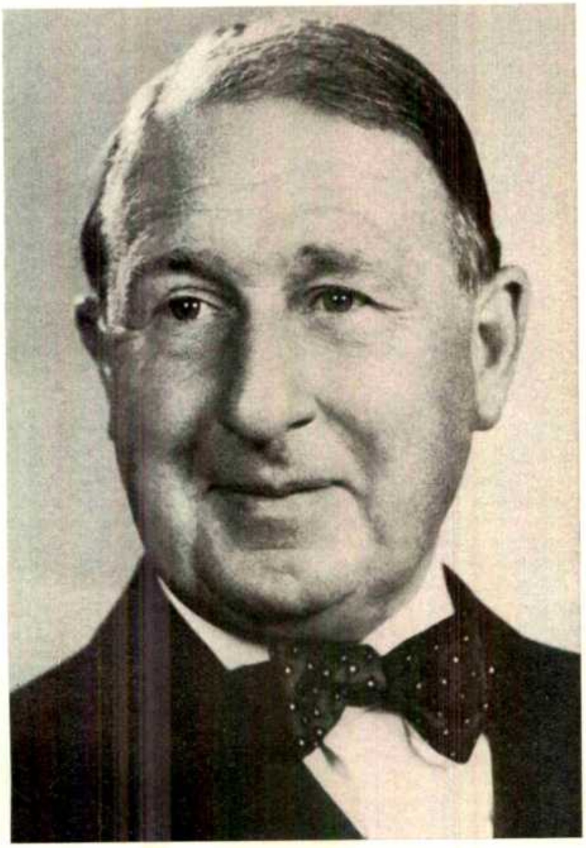
Obituary

S. Whately Davidson, M.D., F.R.C.P., F.R.C.R., F.R.C.R.A.



Dr. S. Whately Davidson, twice a Vice-President of the British Institute of Radiology and a former President of the Faculty of Radiologists, died suddenly on August 30, at the age of 80 years.

Whateley Davidson graduated in 1920. His early ambition was to become a physician and he gained M.D. and M.R.C.P. in 1923. In 1925 he was persuaded by his chief, Dr. (later Sir) William Hume to become Honorary Assistant Physician to the then X-ray, massage and electrical department.

His career in radiology was outstandingly successful and for a long time he dominated the radiological scene in the North-East where he established X-ray services in many hospitals. His principal hospital appointments were to the Royal Victoria Infirmary, the Regional Thoracic Surgery Unit at Shotley Bridge and Newcastle General Hospital.

Dr. Davidson was appointed Clinical Teacher in Radiology in 1925 and Lecturer in Radiology, and Head of the Department when the academic department of the University was formed in 1948.

During the first World War, Whately was a temporary Surgeon Sub-lieutenant in the R.N.V.R. and he maintained his interest in the service, being mobilized in 1938 and stationed first at Chatham then at Aberdeen. He was released a year later for duty in the Emergency Medical Service.

Those with memories of Whately in the 'twenties and 'thirties will recall his work for the Boy Scouts movement in which he rose to high rank, but his energy later was principally diverted to professional spheres.

He was an energetic member of sub-committees to the then Ministry of Health, and was for long an office holder in the B.M.A., culminating in his election to Presidency of the North of England Branch. He played important roles in three international congresses of radiology and, after the formation of the National Health Service, became a regional adviser in radiology and served for six years on the Standing Medical Advisory Committee of the Ministry of Health. Dr. Davidson also played an active role in university affairs in the 1930s when the finding of a Royal Commission led to the union of the College of Medicine and Armstrong College to form the Newcastle division of the University of Durham. In later years the Newcastle division became a separate university.

The Royal Victoria Infirmary, Newcastle, meant much to Whately. He was in charge of the Department of Radiology from 1930 until 1961 and played a very active part in the work of the governing bodies of the R.V.I. (later United Newcastle upon Tyne hospitals).

A lasting memorial to his vision and drive is provided by the present Department of Radiology at the Royal Victoria Infirmary which was planned and built between 1948 and 1952. For over 50 years he ran a private practice which never made inroads on his N.H.S. sessions. At the height of his career in the 1950s his practice must have suffered greatly from the amount of time he spent in London on radiological affairs, for he was a diligent supporter of radiological societies. Whately was an examiner in radiology to many universities and boards. In addition to the high offices he held in the Faculty and the British Institute he was at one time President of the section of radiology of the Royal Society of Medicine. He stood down from Presidency of the British Institute of Radiology as his term of office would have clashed with his Presidency of the Faculty.

His work for the Faculty of Radiologists included a very memorable visit to Australia and New Zealand as an examiner for the F.F.R. He was granted an Honorary Fellowship of the Royal College of Radiologists of Australasia and he was very proud of this.

Whately loved hospital work and he was renowned for his early start at Shotley Bridge where he would arrive before 6.30 a.m. Following his official retirement he continued to visit the R.V.I. to give tutorials to radiological trainees and to lunch in the consultants' dining room where he was a popular figure. He was also almost constantly employed doing locums in the North-East and at the time of his death he was locum consultant radiologist at Gateshead.

Whately's career thus spanned over half a century but his memories of the X-ray Department of the Royal Victoria Infirmary were even longer for he often used to talk of the days when as student, houseman and medical registrar he visited the department.

Whately had a very attractive personality and was beloved by a wide circle of people. He was unfailingly courteous and humane. Although his professional duties carried him away from Newcastle so often, his home and family meant much to Whately. He will be greatly missed by his wife Brenda, his children and grandchildren and a very wide circle of friends and acquaintances.

C. K. WARRICK.

1977, *British Journal of Radiology*, *50*, 156–159

Proceedings of The British Institute of Radiology

Radionuclides in tumour localization and staging*

Abstracts of papers read at a meeting held on February 18, 1976 in the Edward Lewis Theatre, Middlesex Hospital Medical School, London, W.1

Biological mechanisms concerned in the uptake of radiopharmaceuticals by tumours, by D. M. Taylor.
Physical aspects of tumour imaging—a review, by J. Mallard, P. Denby, D. Gvozdanovic, W. I. Keyes and P. F. Sharp.
Clinical considerations in the use of tumour-localizing agents, by M. V. Merrick.
The role of gallium 67 citrate in tumour localization and staging, by A. F. MacDonald.
Indium bleomycin in lymphomas: a small trial with nine months follow up, by K. A. Brownlie and K. E. Britton.
Dynamic imaging in tumour localization, by I. E. Burton, J. H. Todd and R. L. Turner.
Ultrasound and radionuclide imaging of tumours, by D. O. Cosgrove.
Space occupying lesions and the CT scanner, by L. Kreel (*No abstract received*).
Serial brain imaging in assessment of patients during and following radiotherapy for intracranial neoplasms, by Margaret A. Sheppard and J. Stone.
The assessment of regional cerebral function in brain tumour patients by the continuous inhalation of oxygen-15, by T. Jones, C. G. McKenzie, S. Moss, P. D. Buckingham and J. C. Clark.
Value of bone scanning in the staging of breast cancer, by J. M. Henk and S. Kirkman.
Regional lung function in patients with bronchogenic carcinoma before and after radiotherapy, by F. Fazio, T. A. Pratt and C. G. McKenzie.
Short term cultures of human tumours as models for the study of tumour localizing radiopharmaceuticals, by P. P. Dendy.

BIOLOGICAL MECHANISMS CONCERNED IN THE UPTAKE OF RADIOPHARMACEUTICALS BY TUMOURS

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Radiopharmaceutical uptake by tumours is governed by two processes, delivery of the agent to the tumour area and its uptake and fixation in tumour cells. Delivery is influenced by the blood flow and microvasculature of the tumour area; differential uptake of radiopharmaceuticals will depend on how much these parameters differ from surrounding tisues. Microvascular changes which may influence delivery and retention of radiopharmaceuticals in tumours include tumour blood volume, interstitial fluid volume and pressure, lymphatic drainage and vascular permeability.

Fixation of radiopharmaceuticals in tumour cells involves many factors including membrane transport or binding, "tumour-specific" biochemical pathways, phagocytosis and interaction with protein or subcellular organelles. In a few special situations cellular biochemical pathways have been used to obtain useful tumour localization but no truly tumour-specific biochemical function has been identified. Lysosomal structures are important in the fixation of metallic radionuclides, and the uptake of gallium-67 and indium-111 in tumours and normal tissues is governed apparently by the tissue lysosomal activity; macrophages show no great selectivity of uptake compared to tumour cells.

None of these mechanisms can produce tumour-specific uptake of radiopharmaceuticals although several may combine to produce useful differential tumour uptake. Better exploitation of these processes may improve this differential. Tumour-specific uptake may be achievable with labelled anti-tumour antibodies and further work in this area should be rewarding.

PHYSICAL ASPECTS OF TUMOUR IMAGING—A REVIEW

By J. Mallard, P. Dendy, D. Gvozdanovic, W. I. Keyes and P. F. Sharp

Department of Medical Physics
University of Aberdeen

Radionuclide imaging identifies high-risk patients and makes simple a whole body survey for metastases, single and multiple. It is time that staging schemes included scanning results.

The ability to detect a tumour depends on the concentration ratio, the size and depth of the tumour, the accuracy of image formation, and the effectiveness of the display system. The image formation depends on maximizing counts and obtaining good response at high spatial frequencies in phantom: often commercial collimators are not optimal for the latter and it is necessary to measure their properties in phantom. The spatial frequencies which describe the addition of a 2 cm tumour to a brain scan lie mainly in the range 0.2 to 0.6 cycles/cm. Isotope systems behave poorly in this range. More information would be helpful on the volume of tissue from which collimators accept radiation and perhaps the use of edge spread functions would be more meaningful clinically than line spread functions. Imaging efficiency (plane sensitivity divided by area imaged) gives a useful comparison between scanners and cameras.

Psychometric visual perception experiments have demonstrated that multi-level displays make tumours visible at half the contrast of standard oscilloscope displays on gamma cameras, and have shown that the optimum display, which has levels of three standard deviations width, can show tumours which would not be displayed by the normal linear scale. The psychometric technique has shown also that one needs about twice the concentration ratio to see tumours of half the size; that brain scanning conditions require a concentration ratio of 9 and liver scanning conditions of 6 to perceive a 2 cm tumour at 10 cm depth; that coarse resolution collimators are only better than fine resolution collimators for detecting larger tumours; and that processed pictures, when used carefully, are a real improvement for detecting tumours.

Computerized isotope transverse section imaging is of great value in brain scanning, and the considerable gain of contrast found, particularly in liver scanning conditions, makes it most likely that it will enable smaller metastatic deposits to be found. Truly quantitative *in-vivo* measurement of radioactivity can be achieved using transverse section imaging and the technique is expected to complement EMI scanning just as isotopes have always complemented X-rays.

For the future, multiple isotope sections; coded apertures for small objects such as parathyroids, adrenals, metastases; perhaps solid state: natural biochemical labels with carbon-11 and liposomes for the tailor-made tumour seeking radionuclide.

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*Reprints of these abstracts are available free on application to the Managing Editor, British Journal of Radiology, 32 Welbeck Street, London W1M 7PG, telephone 01–935 6867.

Proceedings of The British Institute of Radiology

CLINICAL CONSIDERATIONS IN THE USE OF TUMOUR-LOCALIZING AGENTS

By M. V. Merrick

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Any discussion of the role in clinical practice of tumour localizing agents requires two assumptions to be made. Firstly, that agents exist which in some way localize in malignant tissue, and secondly, that there is a clinical need to do this.

It is clear that the majority of agents used at present to assist in the staging of cancer do not demonstrate malignancy as such, but rather some local physiological derangement secondary to the malignancy. The best example of this is the bone scan, which shows not the tumour but the attempt at repair of damage caused by the presence of a neoplasm. Similarly, the liver scan shows areas of liver replacement but does not give any information about the material or tissue which has replaced reticuloendothelial tissue. The nature of the process which is illuminated by gallium is far from clear, but the fact that gallium accumulates in many inflammatory conditions is good evidence that, whatever this process may be, it is not specific to malignancy.

Physical limitations of the detecting systems available are also an important consideration. Virtually any agent will detect a large peripheral lesion in the lung, but, since this is readily detectable by a simple chest X-ray, such an agent is of no clinical value. In order to detect small lesions in areas such as the mediastinum or abdomen, a tumour-to-background ratio of greater than 18:1 is required and in practice such a ratio is rarely attainable.

The clinical application of these agents is determined both by their inherent limitations and by the limitations of available therapy. There is fairly general agreement that accurate staging is essential in the proper management of Hodgkin's disease. In other diseases there is no concensus. Some clinicians will vary their treatment of, for example, carcinoma of the breast or cervix, depending on the extent of spread, but many others regard detailed staging procedure at present as essentially a research project, *e.g.* for the assessment of treatment régimes rather than for the benefit of the individual patient.

THE ROLE OF GALLIUM 67 CITRATE IN TUMOUR LOCALIZATION AND STAGING

By A. F. MacDonald

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Gallium-67 citrate has been used since 1969 for the detection of malignant tumours and lymphomas. The usual dose of 1 to 3 mCi, with a half life of 78 hours and useful emissions of 93 and 184 keV, results in total body radiation of less than 1 rad. The cost of the isotope is at least £25 per dose.

Because of initial high background activity, scanning is usually delayed for 24 or 48 hours and is carried out with high sensitivity collimators.

Normal uptake is present in liver, spleen, bone and secretory mucosa, and liver excretion results in a high large-bowel content which, despite clearing enemata, considerably limits the diagnostic value in the abdomen. Positive detection rates of up to 90% have been reported in tumours of the bronchus, melanoma and thyroid, but as low as 50% in genito-urinary tract, breasts and gastro-intestinal tract including liver. The diagnostic accuracy of gallium is also severely limited by positive uptake in non-malignant lesions such as granulomata, chronic infections and sarcoidosis.

Organ-specific isotope preparations are usually more efficient than gallium in tumour detection. Gallium is therefore in general use only for the occasional detection of occult tumour but mainly for the diagnosis and staging of lymphoma where its accuracy above the diaphragm and occasional unsuspected sites of involvement including bone is of established value.

Various modifications of technique, such as intralymphatic injection, are currently under investigation, but it is unlikely that the role of gallium will increase in the immediate future.

INDIUM BLEOMYCIN IN LYMPHOMAS: A SMALL TRIAL WITH NINE MONTHS FOLLOW UP

By K. A. Brownlie and K. E. Britton

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Fifteen patients with lymphomas, nine having Hodgkin's disease, were scanned using an El Scint whole body system, either 36 or 48 hours after injection of 2.5 to 3.2 mCi of indium-111 labelled bleomycin.

Positive findings below the diaphragm were found in nine cases, four confirmed by lymphography and/or laparotomy and five unconfirmed at the time of the scan; one of the latter being confirmed at follow up after a year. The other four had nine months follow up without further symptoms. Negative findings below the diaphragm were present in six; four of these failed to show any positive findings on lymphography and/or laparotomy, two not being further investigated. These patients all remained symptom free for the follow-up period. Mediastinal nodes were confirmed to be positive in the two cases demonstrated by scanning, whereas two further cases scanned after radiotherapy were negative. No false positive or negative results for mediastinal nodes were found in the 15 patients.

The key question remains whether the four positive unconfirmed subdiaphragmatic results are true positives and further follow up is continuing. At least a positive result should indicate which node group to biopsy at laparotomy, and three scans were positive when lymphography failed for technical reasons to demonstrate the relevant nodes.

DYNAMIC IMAGING IN TUMOUR LOCALIZATION

By I. E. Burton, J. H. Todd and R. L. Turner

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A series of 52 patients with known squamous cell carcinomata were studied using indium-111–bleomycin. An overall accuracy of tumour localization of 80% was obtained by static imaging. The accuracy varied with site, being most accurate for tumours of the lungs, bronchus and pelvis. Oseophageal tumours were masked by high indium activities in the liver and bone marrow and none of the four cases investigated were detected. False positive areas of increased uptake were also noted on about one in five scans. The most common cause was pneumonia.

The technique of dynamic imaging was used to study the uptake pattern of indium-111–bleomycin in normal squamous tissue, tumour and pneumonia. The maximum concentration of the radiopharmaceutical in squamous cell tumour tissue occurred on average ten minutes after the peak for normal tissue. This difference in uptake curves was used to improve the detection of known tumours to about 90%. Dynamic imaging also showed that the increased activity seen on static scans in pneumonia was due to increased vascularity and not accumulation of bleomycin.

ULTRASOUND AND RADIONUCLIDE IMAGING OF TUMOURS

By D. O. Cosgrove

Royal Marsden Hospital, Sutton

New developments in ultrasonic imaging, notably high resolution with grey scale display, have led to its increasing use in tumour localization. Technical considerations preclude its use in the brain, thorax and skeleton, but elsewhere it has the ability to display fine anatomic structure due to reflection of sound from tissue interfaces.

In the thyroid, ultrasound reliably distinguishes between solid cystic lesions, both of which give "cold" regions on isotope scanning. Reports of differentiation between benign and malignant tumours are promising.

In the abdomen, ultrasound makes an important contribution to assessment of the liver, since it has greater sensitivity than the liver scan together with the ability to discriminate between tumours, benign lesions and focal inflammatory diseases. In addition it clarifies many equivocal liver scintigrams. In practice, the techniques have proved complementary.

Pancreatic ultrasonography has been claimed to be very accurate but in our hands, while the detection of cysts and large masses is simple, small tumours are not detectable.

Isotope imaging of involved abdominal lymph nodes is restricted to tumour types avid for gallium or indium; ultrasonic imaging is possible with any histology providing the abdomen is clear of gas. Regions inaccessible to lymphangiography may also be imaged and details used for radiation planning.

In the pelvis, masses involving the bladder and the reproductive tract can often be imaged ultrasonically, the prostate being a particularly promising target. Only rarely will isotope techniques be helpful here or in the scrotum, another developing ultrasonic field.

SPACE OCCUPYING LESIONS AND THE CT SCANNER

By L. Kreel

Northwick Park Hospital, Harrow, Middlesex

(No abstract received)

SERIAL BRAIN IMAGING IN ASSESSMENT OF PATIENTS DURING AND FOLLOWING RADIOTHERAPY FOR INTRACRANIAL NEOPLASMS

By Margaret A. Sheppard and J. Stone

Regional Radiotherapy Centre
Cookridge Hospital, Leeds

As an aid to clinical assessment of patients undergoing radiotherapy for intracranial neoplasms, brain images using $^{99}\mathrm{Tc}^{m}$ sodium pertechnetate are carried out at intervals beginning before treatment and continuing for up to two years after the end of treatment.

Images are made on a dual headed Ohio Nuclear scanner and measurements are taken both with regard to tumour size on the scan and the average count rate over the tumour area using a densitometer and a calibrated density/count rate ladder. Results are presented graphically with average count rate over tumour compared with normal brain on the affected lateral and also the appropriate area on the opposing lateral. Similar comparisons are made on the anterior and posterior views comparing the tumour area with the opposite side and also the superior sagittal sinus.

The period and frequency with which patients are investigated are dependent on the physical state of the patient. Patients are assessed objectively at follow-up clinics, either as out-patients or on admission if undergoing chemotherapy.

In general, tumour size and uptake decrease between the beginning and end of treatment and patients show a clinical improvement.

Measurement of tumour to brain ratio tends to give an earlier indication of patient deterioration than pure clinical follow-up.

Measurement of tumour size on scans after radiotherapy is a reliable indicator of the progress of the patient.

We are in no doubt that measurements of tumour to brain ratios can give information regarding the state of the patients which would otherwise not be available at that time.

THE ASSESSMENT OF REGIONAL CEREBRAL FUNCTION IN BRAIN TUMOUR PATIENTS BY THE CONTINUOUS INHALATION OF OXYGEN-15

By T. Jones, C. G. McKenzie, S. Moss,
P. D. Buckingham, and J. C. Clark

MRC Cyclotron Unit, Hammersmith Hospital
Ducane Road, London, W.12

To assess the results of radiotherapy on brain tumours objectively it would be appropriate to study the regional uptake of oxygen in both the cerebral and tumour tissues serially. This concept has been approached by the subject continuously inhaling gamma emitting oxygen-15 (2.1 minute half life) while the isotope is being continuously produced by the cyclotron. Following six minutes of inhalation, the radioactivity in the brain, which has a dependence on both regional oxygen extraction and blood flow, reaches a steady state (Jones *et al.*, 1976). At this point the cerebral distribution of oxygen-15 is imaged with an Anger gamma camera. Tumours are generally shown as areas of decreased oxygen-15 uptake within the brain image. When following patients during radiotherapy variable responses have been observed, there being a general correlation between clinical improvement and a reduction in the size of the low uptake area. In order to resolve whether regions of decreased uptake are the result of low oxygen extraction or blood flow, an additional image is recorded while oxygen-15 labelled carbon dioxide is inhaled. This second procedure reproduces the blood flow components present in the brain image obtained while inhaling oxygen-15. The difference in in the $^{15}O_2$ and $C^{15}O_2$ images is directly related to variation in tissue extraction of oxygen (Jones *et al.*, 1976).

REFERENCE

JONES, T., CHESLER, D. A., and TER-POGOSSIAN, M. M., 1976. The continuous inhalation of oxygen-15 for assessing regional oxygen extraction in the brain of man. *British Journal of Radiology*, *49*, 339–343.

VALUE OF BONE SCANNING IN THE STAGING OF BREAST CANCER

By J. M. Henk and S. Kirkman

Velindre Hospital, Cardiff

Bone scans with technetium phosphate compounds were performed on 514 patients with carcinoma of the breast referred to the South Wales Radiotherapy Centre for treatment in 1973 and 1974. Abnormal scans were deemed positive where the X-rays confirmed the presence of metastases or where there was no benign skeletal lesion to explain the abnormality. Seventy-nine patients had positive scans with normal X-rays. Follow-up showed that the majority of these soon developed radiological evidence of bone metastases; an actuarial prediction of 86% confirmed at two years was made.

Two hundred and eighty-four patients had normal scans. Only nine (3%) developed evidence of bone metastases during the first year after scanning. Bone metastase were demonstrated on the scan in 13% of patients who had no clinical or radiological evidence of blood-borne metastases. The highest detection rate was in Stage III, 22%; post-operative and local recurrent cases both showed a detection rate of 12%.

It is concluded that the bone scan could usefully replace the skeletal survey as a routine in the staging of breast carcinoma, provided that any sites of abnormal uptake are X-rayed routinely.

REGIONAL LUNG FUNCTION IN PATIENTS WITH BRONCHOGENIC CARCINOMA BEFORE AND AFTER RADIOTHERAPY

By F. Fazio, T. A. Pratt and C. G. McKenzie

Departments of Medicine, Diagnostic Radiology
and Radiotherapy, Hammersmith Hospital
London, W.12

Combined ventilation-perfusion ($\dot{V}/\dot{Q}$) scans in multiple views have been obtained in 33 patients with inoperable hilar bronchogenic carcinoma using the ^{81m}Kr inhalation technique for ventilation and ^{99}Tc^{m} microspheres for perfusion. In 20 patients $\dot{V}/\dot{Q}$ scans were repeated after a course of supervoltage radiotherapy. Both $\dot{V}$ and $\dot{Q}$ scans were scored with a 9 points scale for each lung. Only one patient showed normal $\dot{V}$ and $\dot{Q}$. Before treatment half of the patients showed, on the side of the tumour, a reduction in perfusion of 75% or more and a reduction in ventilation of 50% or more. Such gross changes in both $\dot{V}$ and $\dot{Q}$ were generally not expected from the chest X-rays and the standard lung function tests. The fact that perfusion tends to be systematically more impaired than ventilation is more in favour of invasion or compression of pulmonary blood vessels, although, at least in some cases, it might be the consequence of a primary reduction in ventilation.

Radiotherapy improves regional ventilation in 68% of the treated patients and regional perfusion in 59%. If the group with the more severe functional impairment (more than 50% impairment of either $\dot{V}$ or $\dot{Q}$ in the affected lung) is considered separately, the effect of radiotherapy appears to be even more remarkable: 90% of these patients show improvement in perfusion and 80% in ventilation. It is concluded that radiotherapy leads to a considerable improvement in regional lung function in most patients with hilar bronchogenic carcinoma. This can explain the discrepancies observed in these treated patients between relief of symptoms (especially dyspnoea) and the lack of gross changes in chest X-rays and lung function tests.

SHORT TERM CULTURES OF HUMAN TUMOURS AS MODELS FOR THE STUDY OF TUMOUR LOCALIZING RADIOPHARMACEUTICALS

By P. P. Dendy

Department of Medical Physics
University of Aberdeen

The ability of different human tumours to concentrate a given radiopharmaceutical appears to be very variable. Very little work has yet been done on the causes of this variation.

A similar variability has been noted in the response of solid tumours to chemotherapy. In the latter case, investigations have been made to find out if these different responses represent variability at the cellular level. Human tumour biopsy material can be maintained in short term culture by a variety of methods; for example, total enzymatic digestion followed by resuspension of the cells in culture medium permits cell monolayers to be grown. Studies on cells blocked in mitosis with colcemid show abnormal DNA values so these are not normal cells cultured from the stroma.

Quantiative methods, based on uptake of isotopically labelled specific precursors of DNA synthesis, indicate that cultures prepared from different tumour biopsies show a wide range of sensitivities to several cytoxic drugs. A limited retrospective clinical trial, based on 63 patients, suggests that during the first 12 months at least, when chemotherapy is based on the test, remissions are better than when chemotherapy is prescribed without the benefit of test predictions.

The use of this *in vitro* model system might improve our understanding of the mechanism of uptake of certain radiopharmaceuticals and this information might permit a more rational choice of scanning agent for each particular patient.

1977, *British Journal of Radiology*, *50*, 160

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

B.I.R. LIBRARY

The opening of the Institute's house for members to use the Library on Saturday mornings has been discontinued through lack of support. However, arrangements would be made for the Library to be opened between 10 a.m. and 1 p.m. on a Saturday if prior notice was given. Telephone 01–935 6237 or write to the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Health Equipment Information, No. 66, carrying news of equipment evaluation trials and of incidents involving defective or misused equipment is devoted entirely to items about radiological equipment. This publication is issued by the Supply Division of the D.H.S.S. Copies of the above available only to N.H.S. staff, should be obtainable from the local administration.

RADIOISOTOPE INVESTIGATIONS OF DISEASES INVOLVING THE ENDOCRINE ORGANS

An all-day meeting held jointly with the Endocrinology Society and organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on February 16, 1977 at the Middlesex Hospital Medical School, London, W1. Registration details and further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

UNORTHODOX APPROACHES TO FRACTIONATION

A meeting held jointly with the Royal College of Radiologists and the Royal Society of Medicine (Section of Radiology) on February 18, 1977. Information from the General Secretary, The British Institute of Radiology.

NEW LEGISLATION FOR RADIOLOGICAL PROTECTION

A meeting to be held at the Middlesex Hospital Medical School on Wednesday, February 23, 1977 arranged by the Association of University Radiation Protection Officers (AURPO) in collaboration with the British Radiological Protection Association (BRPA). Eleven papers will be presented under the Chairmanship of Dr. G. N. Ardran.

Further information is available from Miss T. Brougham, University of Manchester Radiological Protection Service, 327 Oxford Road, Manchester M13 9PL.

9TH INTERNATIONAL DIAGNOSTIC COURSE IN DAVOS SWITZERLAND—HEART AND LUNG

Sponsored by European Association of Radiology. To be held on March 27–April 2, 1977.

Further information and registration please contact IDKD 9, Postfach 2132, CH–8028 Zurich, Switzerland.

THE BRITISH INSTITUTE OF RADIOLOGY ANNUAL CONGRESS AND SCIENTIFIC EXHIBITION

To be held on April 14–15, 1977 at the R.I.B.A., 66 Portland Place, London W1. Papers presented will include the "Silvanus Thompson Memorial Lecture" by Mr. G. N. Hounsfield, C.B.E., of EMI Central Research Laboratories.

Further information and registration from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

RADIATION PROTECTION: AN EXAMPLE OF ACTION AGAINST MODERN HAZARDS

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P., no. 33, 92260 Fontenay-aux-Roses, France.

THE MACKENZIE DAVIDSON MEMORIAL LECTURE

To be given by Dr. David Ingvar, University of Lund on May 19, 1977 at The British Institute of Radiology.

NEW HORIZONS IN INTENSIFYING SCREEN TECHNOLOGY

An all-day meeting organized by the Industry Committee of The British Institute of Radiology on May 20, 1977 at the Middlesex Hospital Medical School, London, W1. Registration details and information from the General Secretary, The British Institute of Radiology.

EXPERIMENTAL AND CLINICAL APPLICATIONS OF KRYPTON 81M

An all-day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology to be held at the Middlesex Hospital Medical School, London, W1 on June 3, 1977. Registration and details from the General Secretary.

HYPOXIC CELL SENSITIZERS IN RADIOBIOLOGY AND RADIOTHERAPY

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV INTERNATIONAL CONGRESS OF RADIOLOGY

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colegio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

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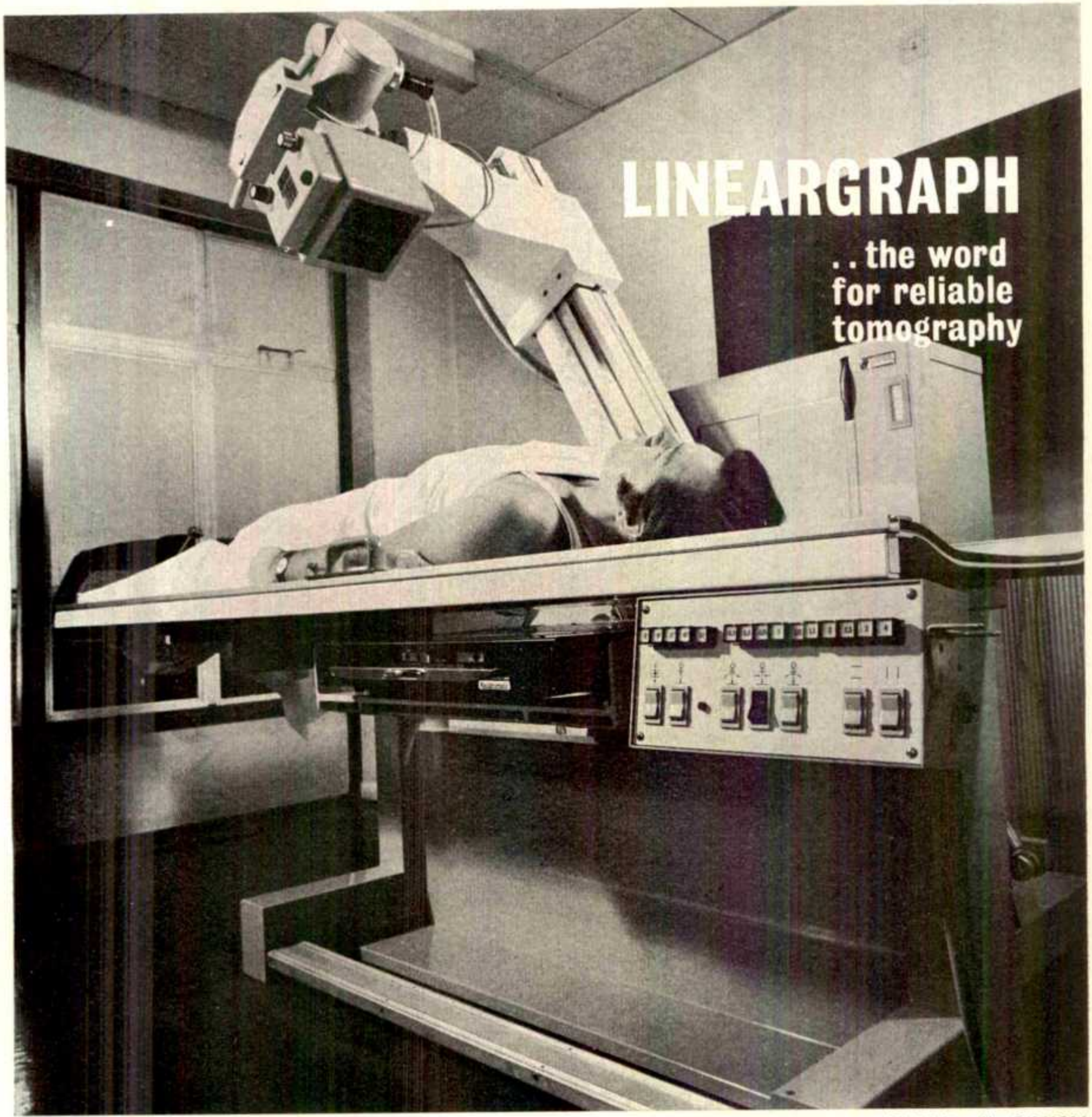

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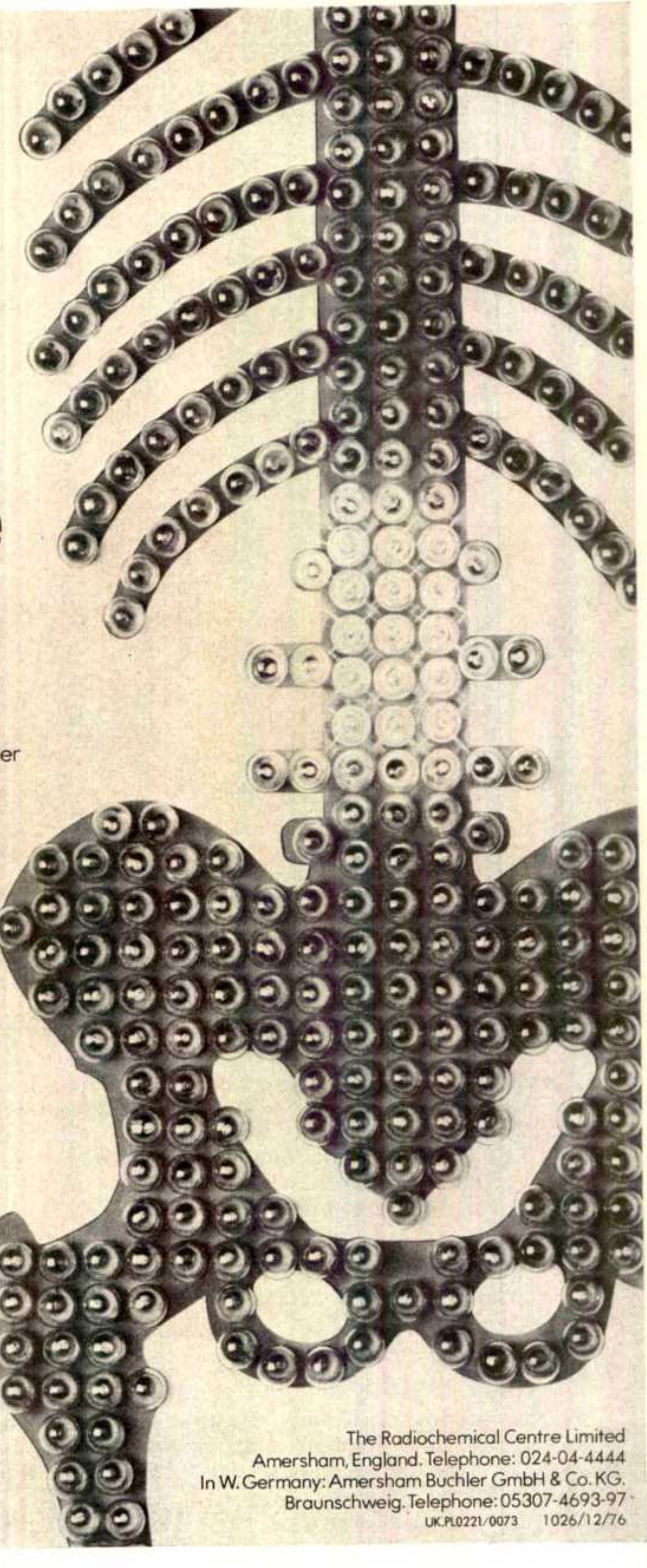

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(1) Subramanian *et al*, *J. Nuc. Medicine*, vol. 16, pp. 744-755, 1975.

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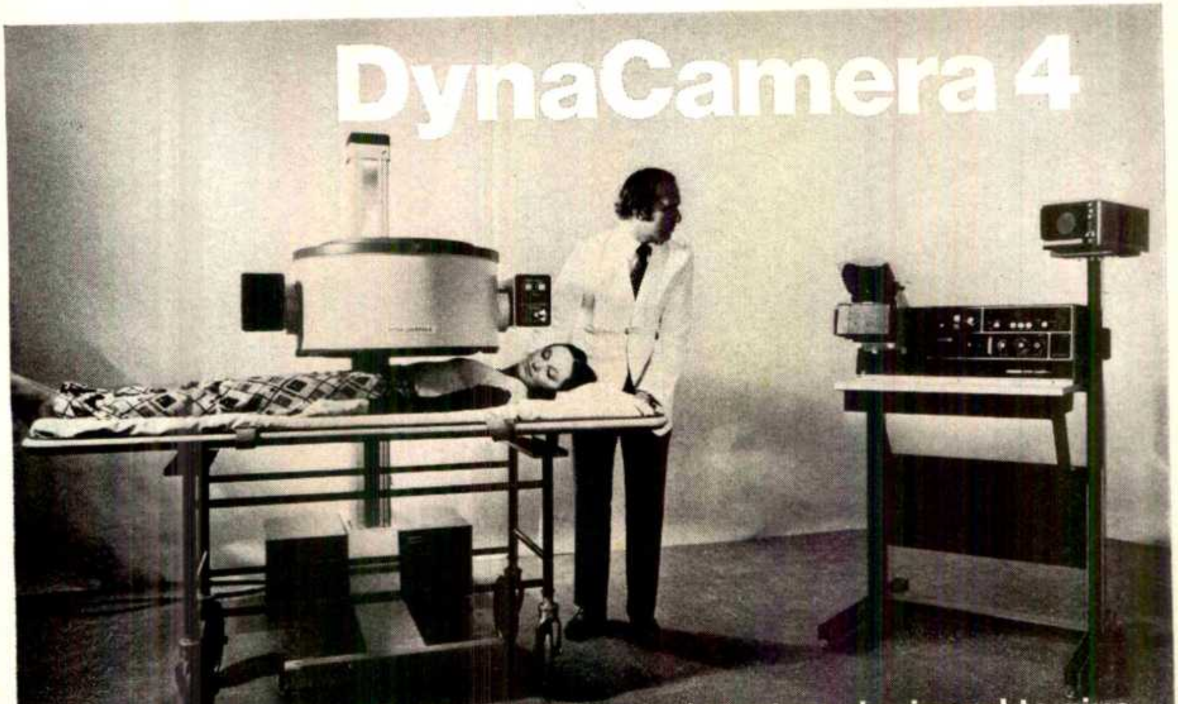

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- Joystick control of the calibrated region of interest for count density quantitation of normal vs. abnormal areas of the patient's organs
- Built-in patient anatomical landmarking system

All items are standard, built-in and exclusive features.

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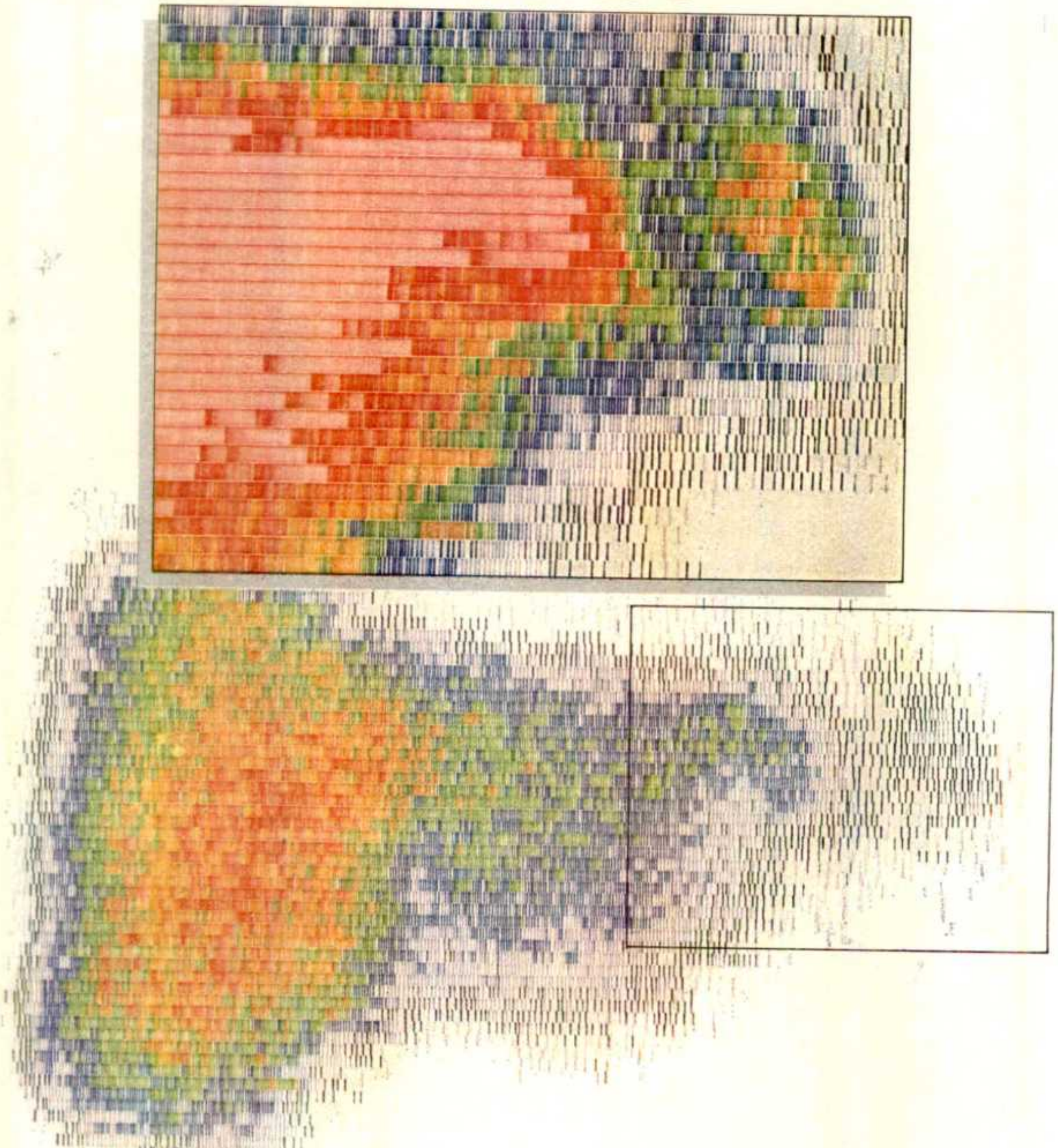
Rapid evidence



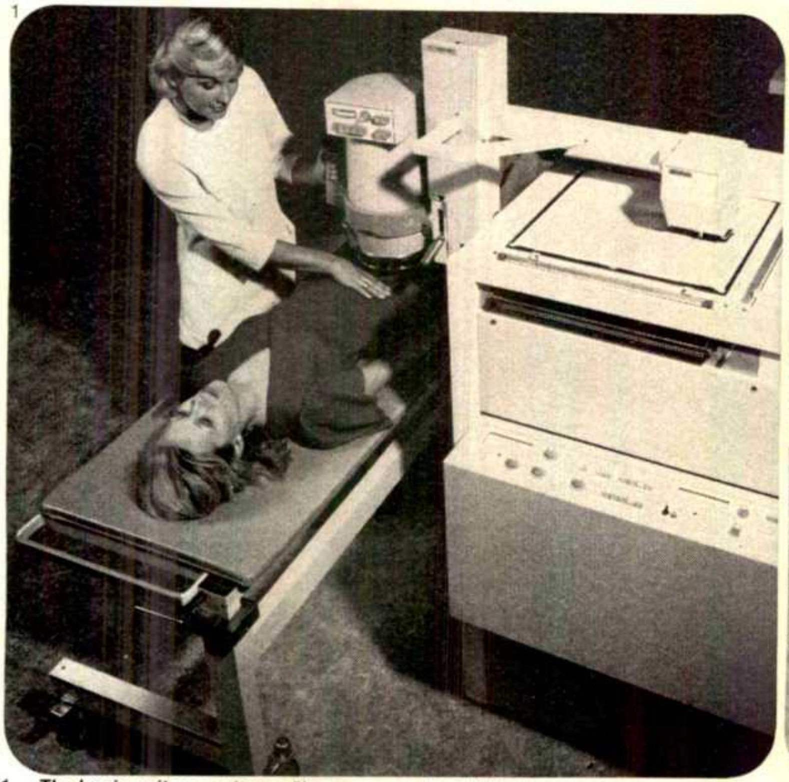
PHILIPS Medical Systems

The lower of the two scintigrams shown here is a 42 x 42 cm liver scan. The other is a detail of that scan, reproduced to the same field size and with enhanced contrast to reveal otherwise indiscernable evidence of the spleen. Rapidly. Both scintigrams were made on a Philips Universal Scintillation Scanner.

The ability to reproduce comparable scans of total organs, with optimum contrast for regions of interest and without the necessity for time-consuming operational adjustment, is a unique feature of the Philips scintillation scanner.

Based on modular design principles, add-on facilities considerably extend the scanner's basic capabilities to suit a wide variety of applications in nuclear medicine – from routine to research. Here's how:

1



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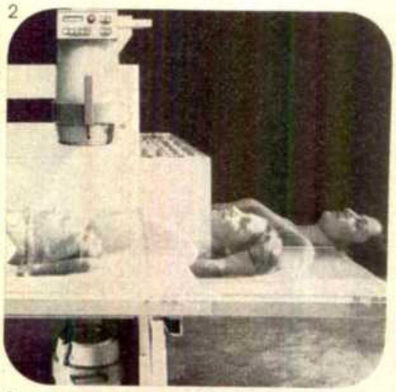

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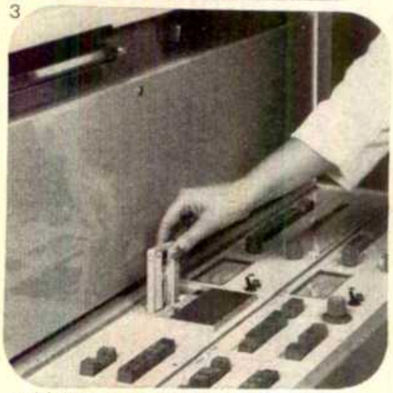

1 **The basic unit** comprises a 5in. overtable detector with motor-driven vertical adjustment of the detector head allowing virtually any patient table or hospital bed to be used.

Ten preselected nuclide settings are provided as well as line interval selection and colour printer and photo scan adjustment and metering. A light beam pointer in the collimator enables the central axis to be accurately positioned. Scanning speed adjustment is continuously variable up to 75mm/s (450 cm/min or approx. 3in./s). All control functions are optimised and strategically positioned to ensure an exceptionally high degree of operational efficiency and safety.

2 **Total body and profile scanning** can also be performed by means of an optional motor-driven tabletop. This enables two-speed longitudinal movement of 100mm/min (approx. 4in./min) and 200mm/min (approx. 8in./min) and facilitates profile scanning using slit collimators. With the total body version the scanning area is 400 x 1600mm (15¾in. x 63in.); scintigram reduction factor being 4:1.

An optional under-table measuring head can be added which, together with a scan control unit, enables pulse sum scanning and β + coincidence scans to be obtained.

3 **A second colour printer and photo scan unit** considerably extends the versatility of the Philips Universal Scintillation Scanner by enabling other original scans, based on different parameters, to be obtained. Furthermore, recording and storage of original scanning data can be achieved by means of a four track compact-cassette recorder. In the playback mode recordings can be reproduced using different scanner settings, i.e. different colour printer control signals.

Part of a complete programme of nuclear medicine equipment and systems, and fully supported by an international service organisation, the Philips Universal Scintillation Scanner represents the perfect integration of operational simplicity and efficiency with applicational flexibility and reliability.

COUPON

If you would like further evidence on Philips Scintillaton Scanner, or on any other equipment in our nuclear medicine programme, complete the coupon and send to: Philips Industries Medical Systems Division, Building QM, Room 326, Eindhoven, The Netherlands

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Effective planning for radiation therapy often requires complex calculations – calculations which are extremely time-consuming, even when centralized computer services are used.

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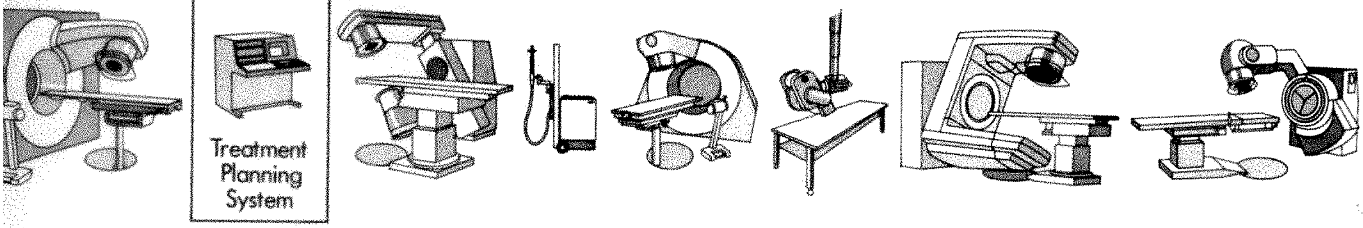
Working with the Treatment Planning System requires no specialized training in computer operation. The user is led step-by-step through the planning procedure, and can change or correct parameters at every stage – with immediate visualization of the results – to arrive at the optimum three-dimensional treatment plan.



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Philips Integrated Therapy Programme

If you would like to know more about the Philips Integrated Therapy Programme, please write to:
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P.A.D. Manor Royal, Crawley, Sussex, England, or Philips Medical Systems Ltd., 45 Nightingale Lane, London SW12 8SX.

PHILIPS

PHILIPS **Medical Systems**

Major requirements in paediatric radiology...

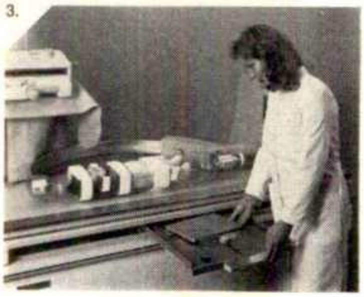
Though varying greatly in size, neonates and adolescents both belong to the domain of the paediatric radiologist, thus special requirements are imposed on the radiological equipment used.
In the case of newborns, accurate positioning and short exposure times are of primary importance. Some older children are already of adult size. This again, imposes other requirements.

...now recognised by Philips ....

1.

2.

3.



1. The change-over from examinations in adults to children is quite literally a matter of seconds. The paediatric supports are quickly installed and removed; parking when not in use is easy and convenient.
The supports are mounted on a column inserted into a permanently installed footrest; this latter feature greatly facilitates the change-over procedure whilst ensuring maximum safety.

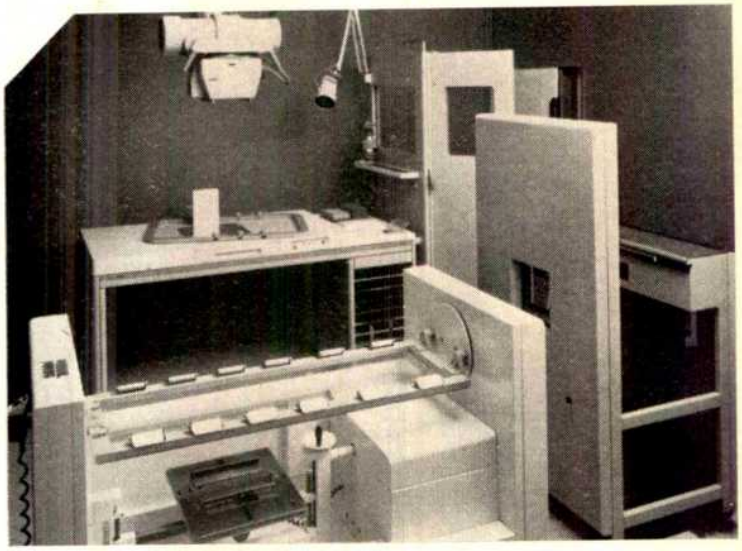
2. The assembly can be moved in its entirety towards and away from the tabletop by motordrive. In this way a short object-film distance and a longer focus-object distance are obtained for serial changer radiography and image intensifier fluorography. As a result images are sharp and the radiation dose to the patient is minimum.

3. The serial changer parks aside, clearing the tabletop for bucky work with an over-table tube.

in two largely complementary X-ray systems which, together, ideally meet all these requirements:

The Junior DIAGNOST System - a special paediatric system for the radiography of patients up to some seven-years "tall". Rapid, convenient patient positioning, excellent image quality are among the outstanding features of this system. In essence, the Junior DIAGNOST comprises three separate stands: one for thorax studies, one for general radiography and the third for tomography. They are operated from a single, ceiling-suspended X-ray tube powered by a single, high-output H.T. generator. The entire system fits neatly into one small examination room.

The DIAGNOST 73 P - a dedicated paediatric system for fluoroscopic and radiographic examinations in children regardless of their age or size. At the same time, however, it offers all the facilities of a universal X-ray system. The ancillary equipment for the DIAGNOST 73 P includes easily fitted supports for babies, for children from two to about six years and also a set of special supports for use in pneumo-encephalography and urology.



....and met to the full at Karolinska Sjukhuset.

The systems can be seen in everyday use in the Children's X-ray Department of Karolinska Sjukhuset in Stockholm. They were installed some time ago, and the personnel have now become thoroughly familiar with their operation.

For lectures describing clinical experience with the systems, given during the 13th Meeting of the European Society of Pediatric Radiology, and descriptive brochures on the systems contact

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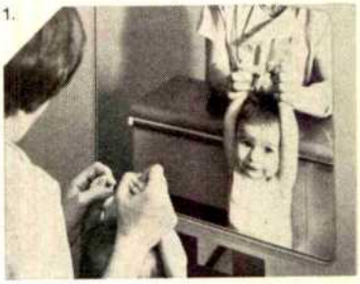
Medical Systems

1.



1. Thorax studies are easily made with the Junior DIAGNOST V.
A footswitch enables the exposure to be triggered exactly at the correct respiratory phase. The collimator has been designed to ensure that stray radiation reaching the hands of the radiographer is kept to the safe minimum.

2.

2. In the case of the Junior DIAGNOST H, positioning is simplicity itself - the tray is moved and not the child.
The extremely short object-film distance of approx. 9 mm results in excellent image quality.

3.

3. Tomography with the Junior DIAGNOST T can be performed with the stand horizontal, vertical or in any intermediate position.
The tomographic effect is produced by a combined movement of patient support and film cassette with the X-ray tube remaining stationary. The very short time required to complete the blurring movement viz. 0.01 sec. per 4 degrees of arc solves the problem of immobilisation.

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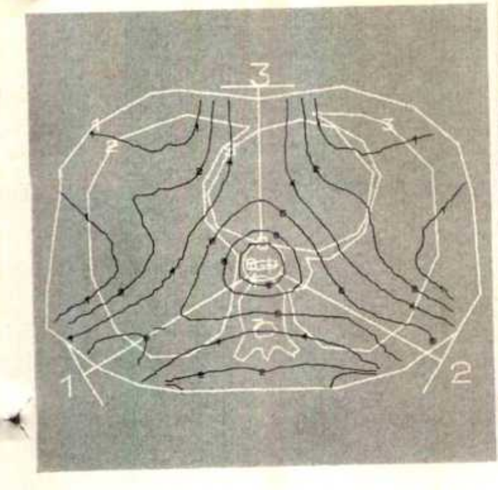

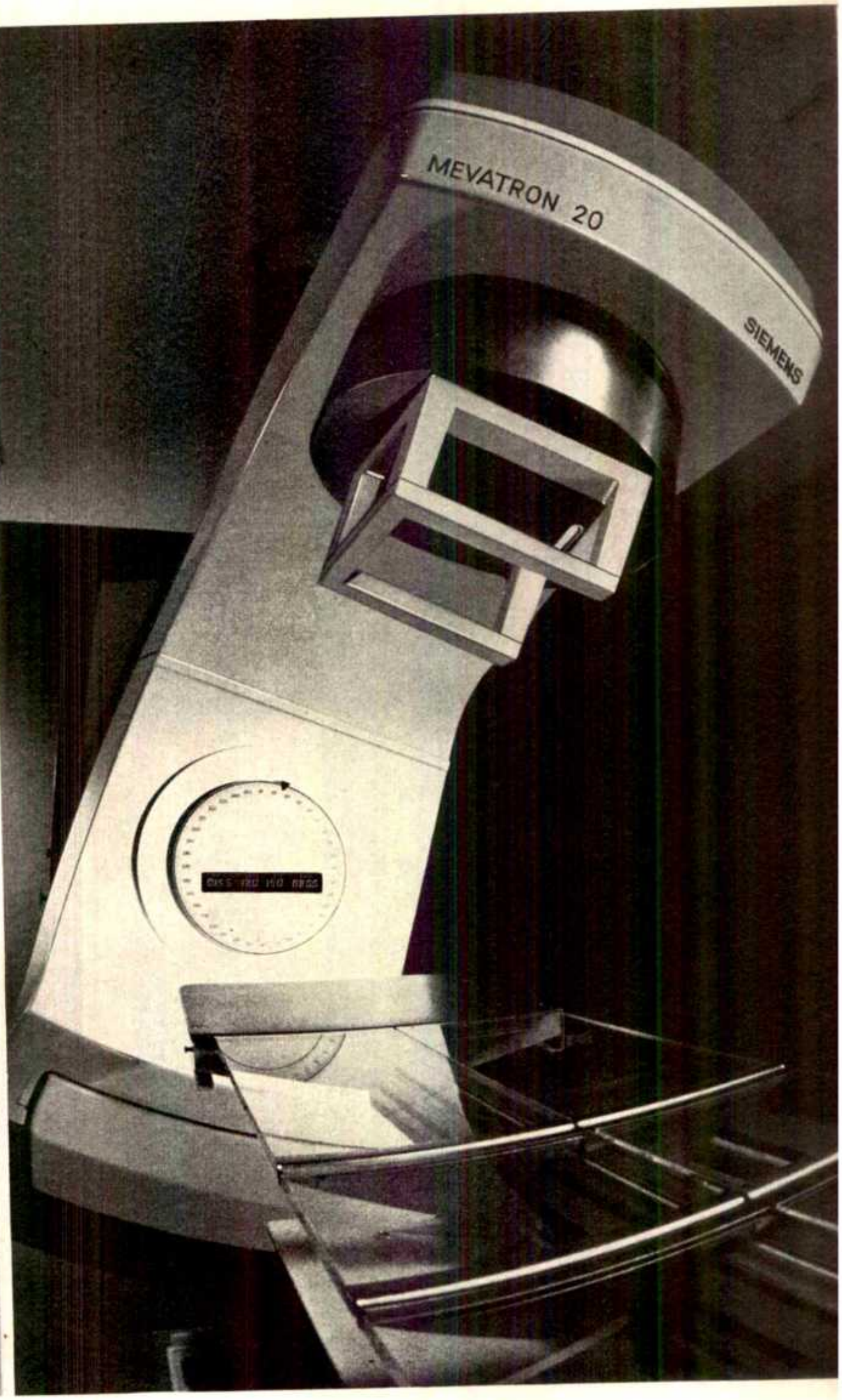

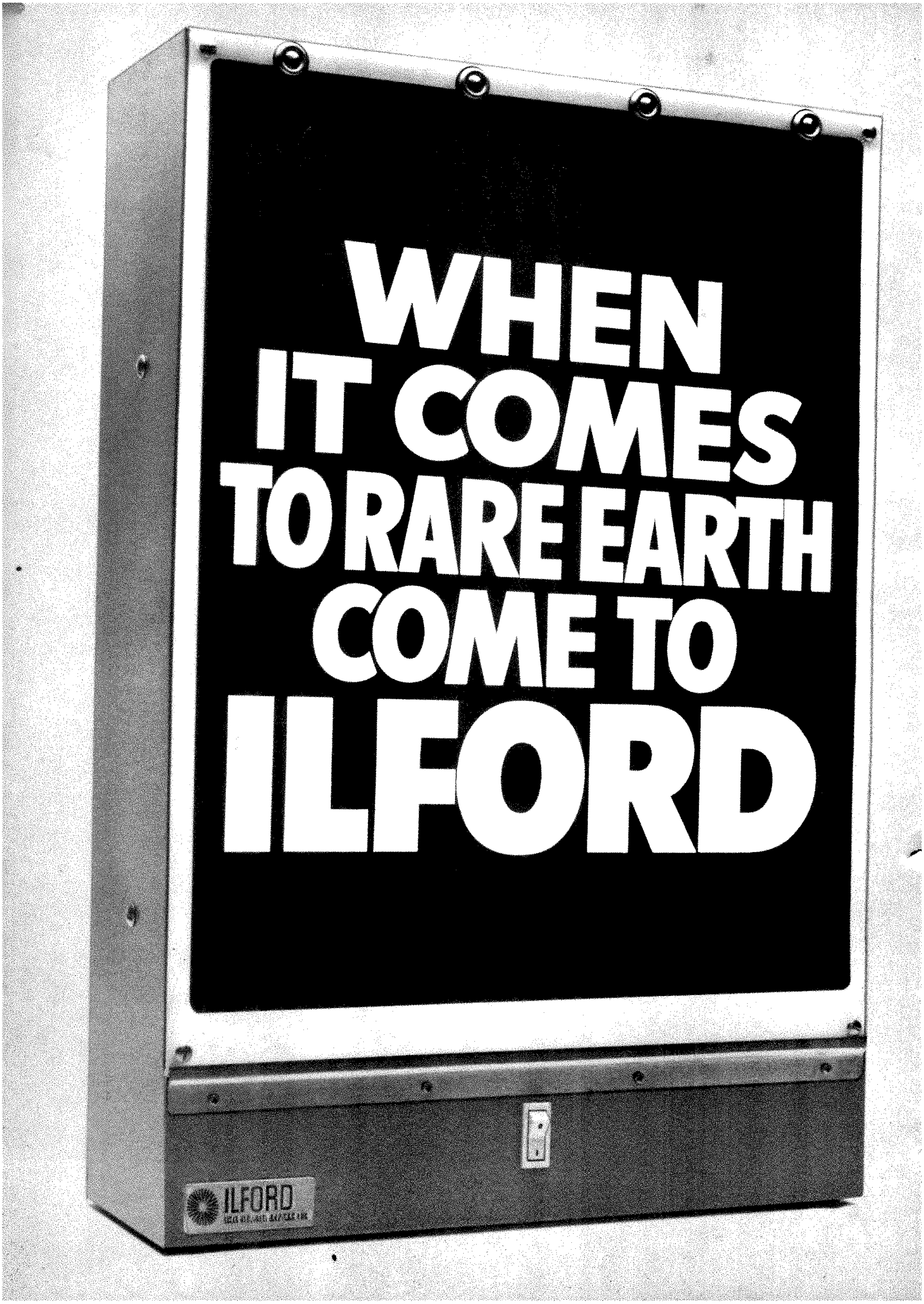
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Apart from reduced radiation risk, the most remarkable factor is the amazing versatility that can be achieved.

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But there's more to it than that.

These new Rare Earth products are an integral part of our total system.

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RAPIDE Screen plus RAPID E	2X	50%
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All you do is change the screens.

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In fact, the perfect blend of our technology and your skill.

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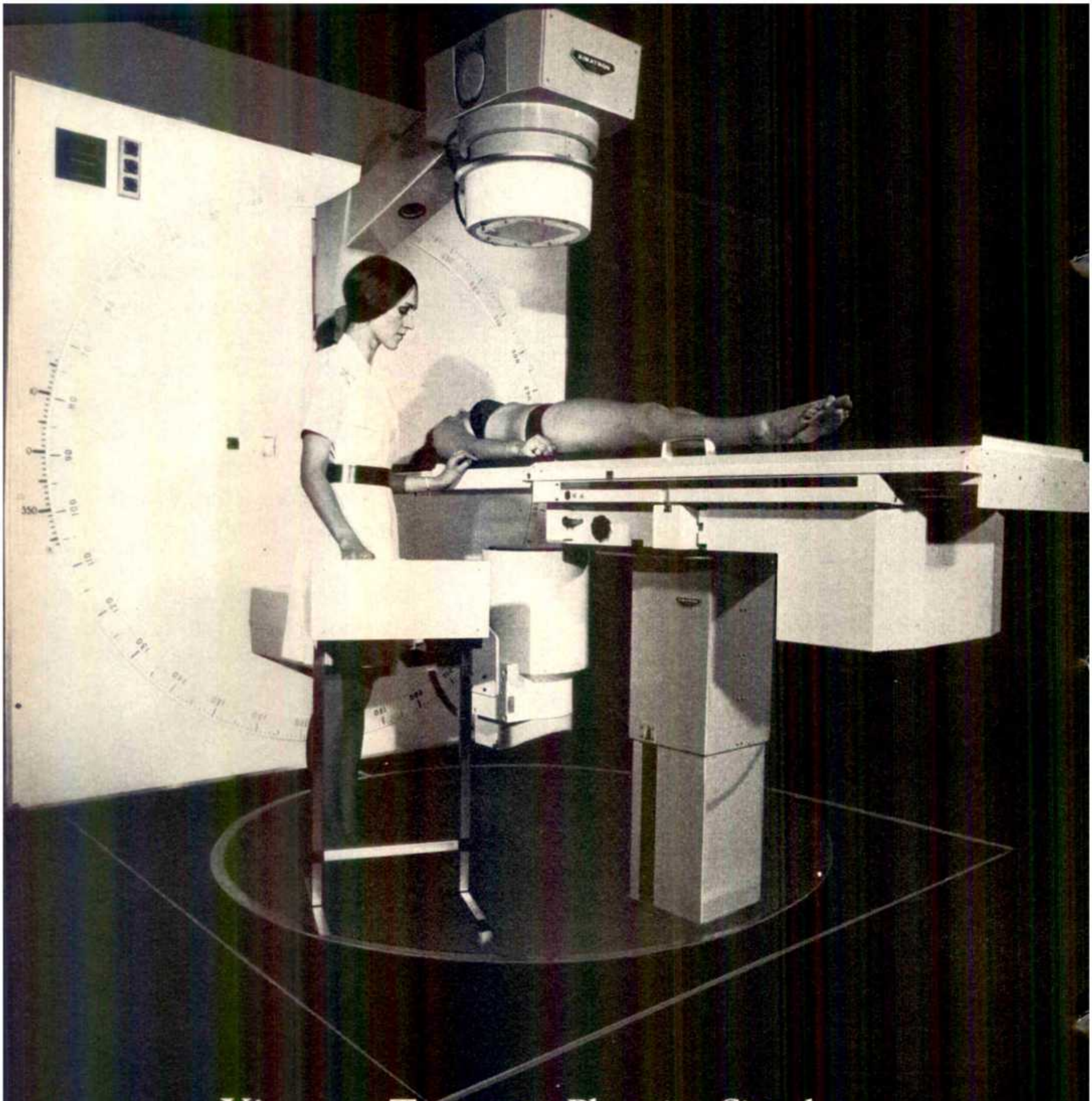

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The ability to simulate the treatment techniques possible from the various treatment units the radiotherapist has at his disposal, is greatly enhanced with the use of the "Ximatron" treatment planning simulator having many new and improved features.

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Motorised wire collimator giving 50 x 50 cm. field at 100 cm.

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The well-known TEM moving spine table top is incorporated with the Ximatron as standard. To allow the operator to rapidly position the patient, manual movement of the table top is provided.

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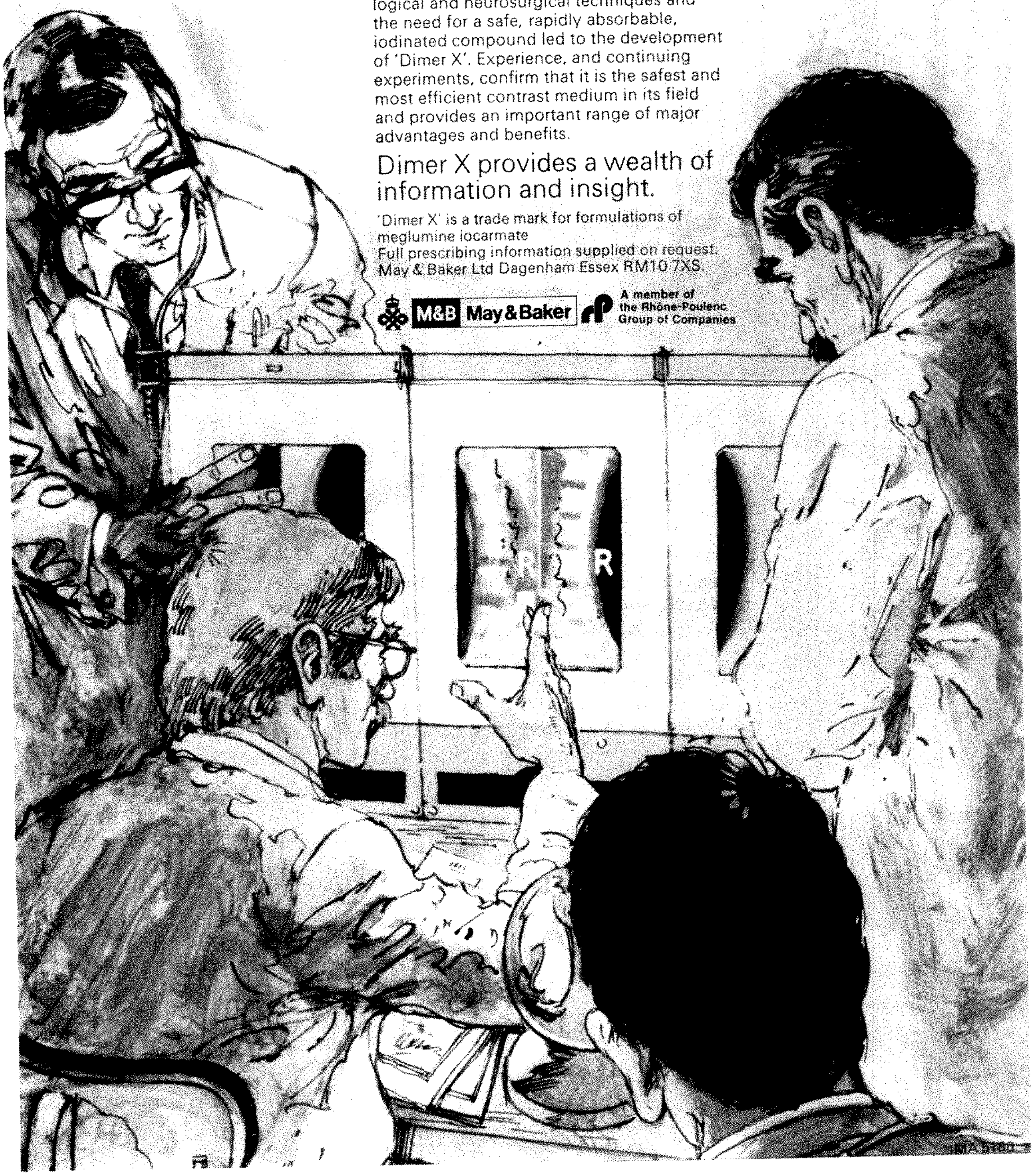
TEM Instruments Limited



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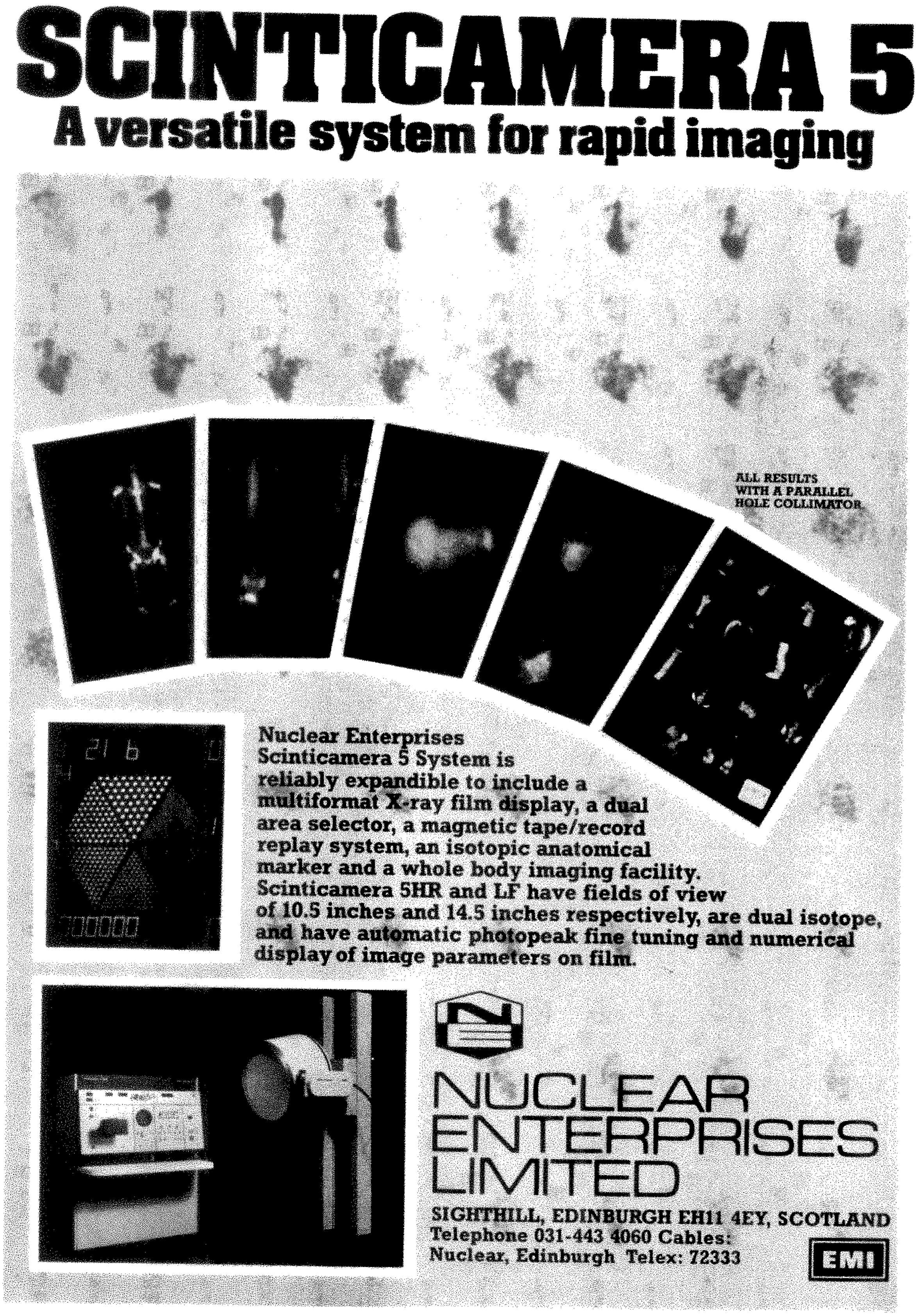

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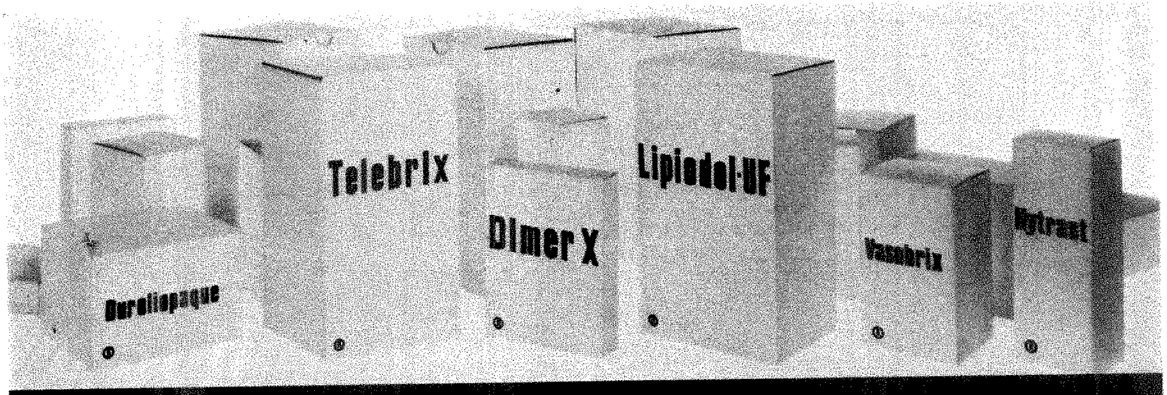

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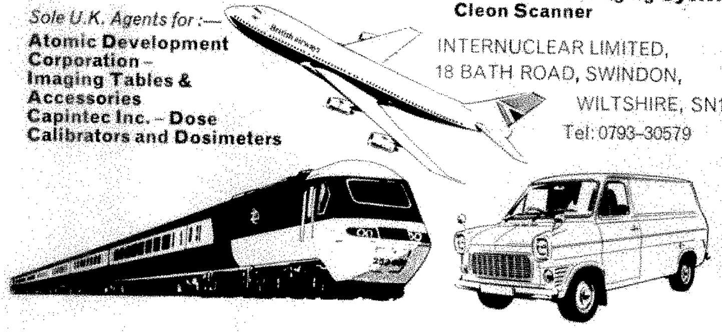

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Warrnambool & District Base Hospital

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RADIOLOGIST POSITION

There is a vacancy for a second Radiologist in the Warrnambool and District Base Hospital.

Duties are to assist in providing a radiology service to the city of Warrnambool and surrounding areas, the total population being in the vicinity of 60,000 people.

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CONDITIONS:

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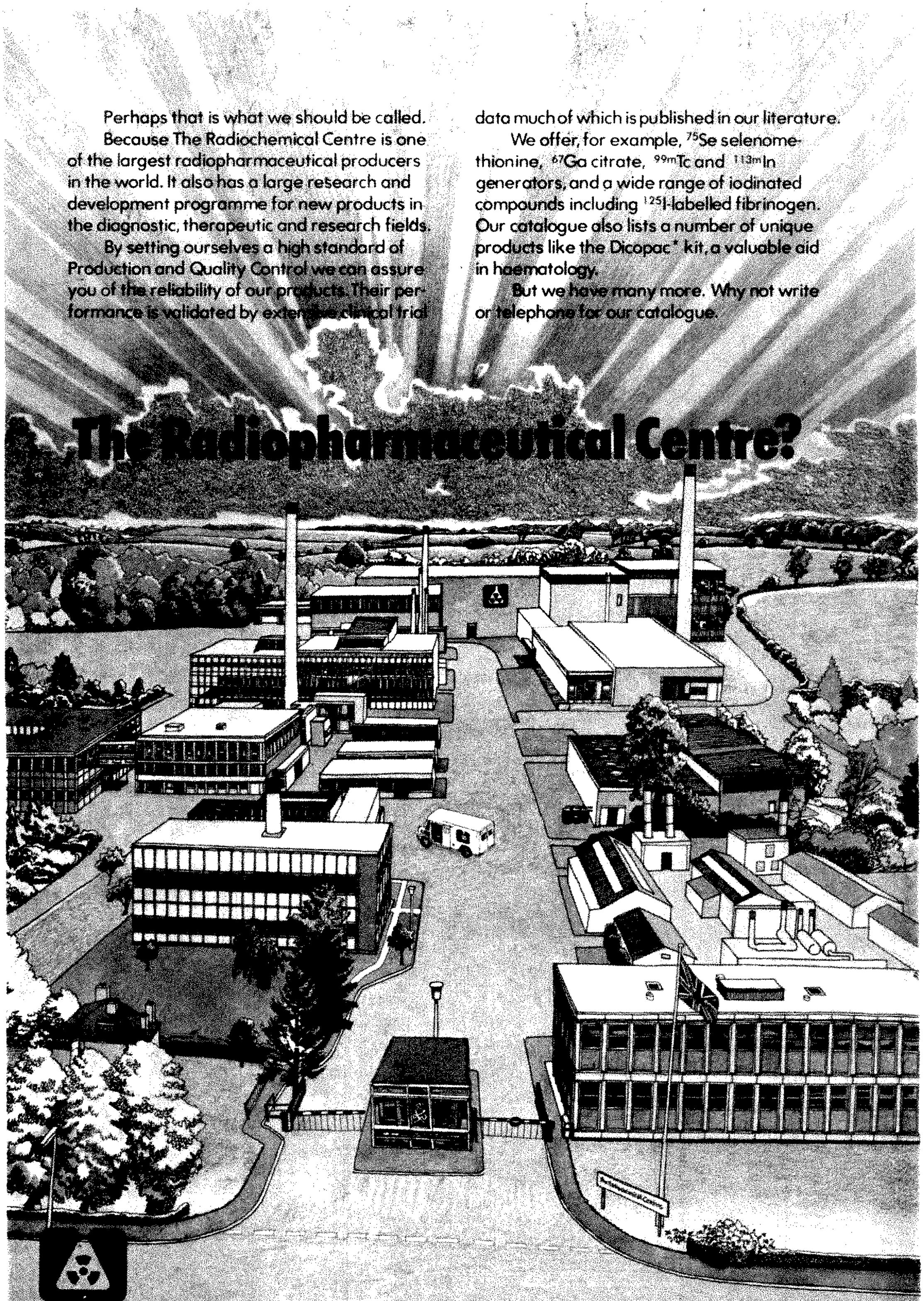

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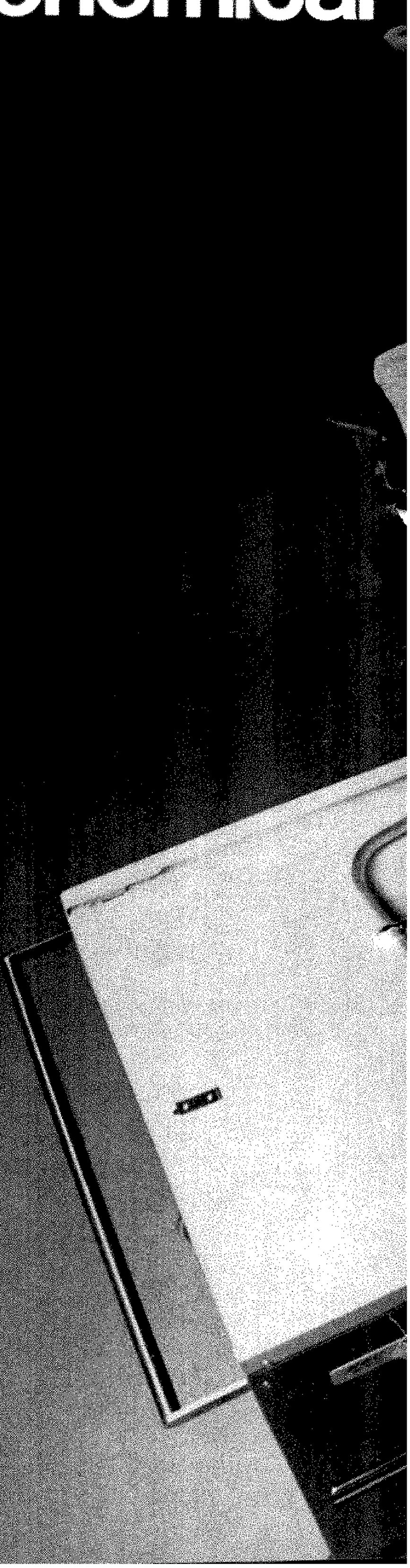

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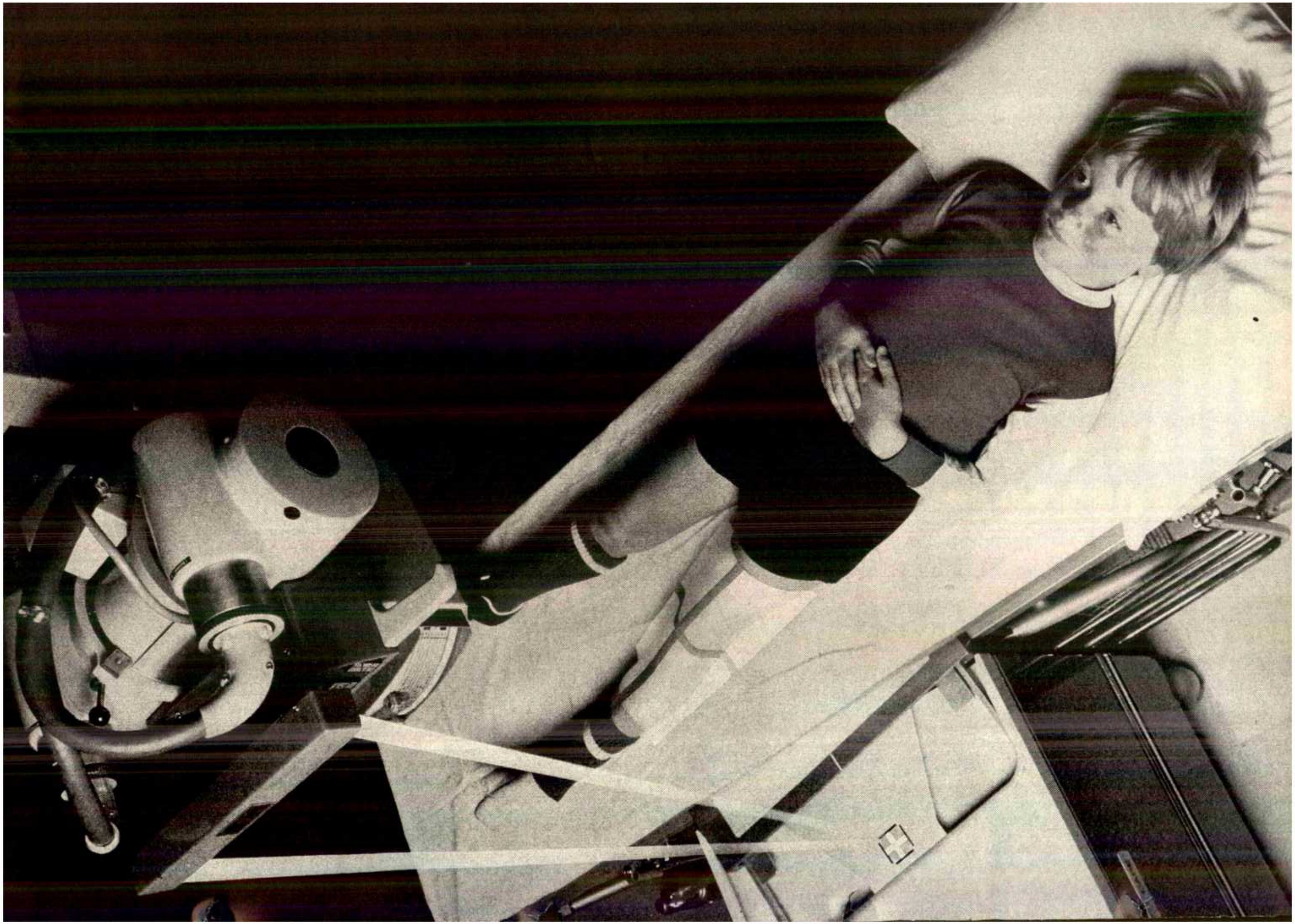

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for pneumoencephalography in a
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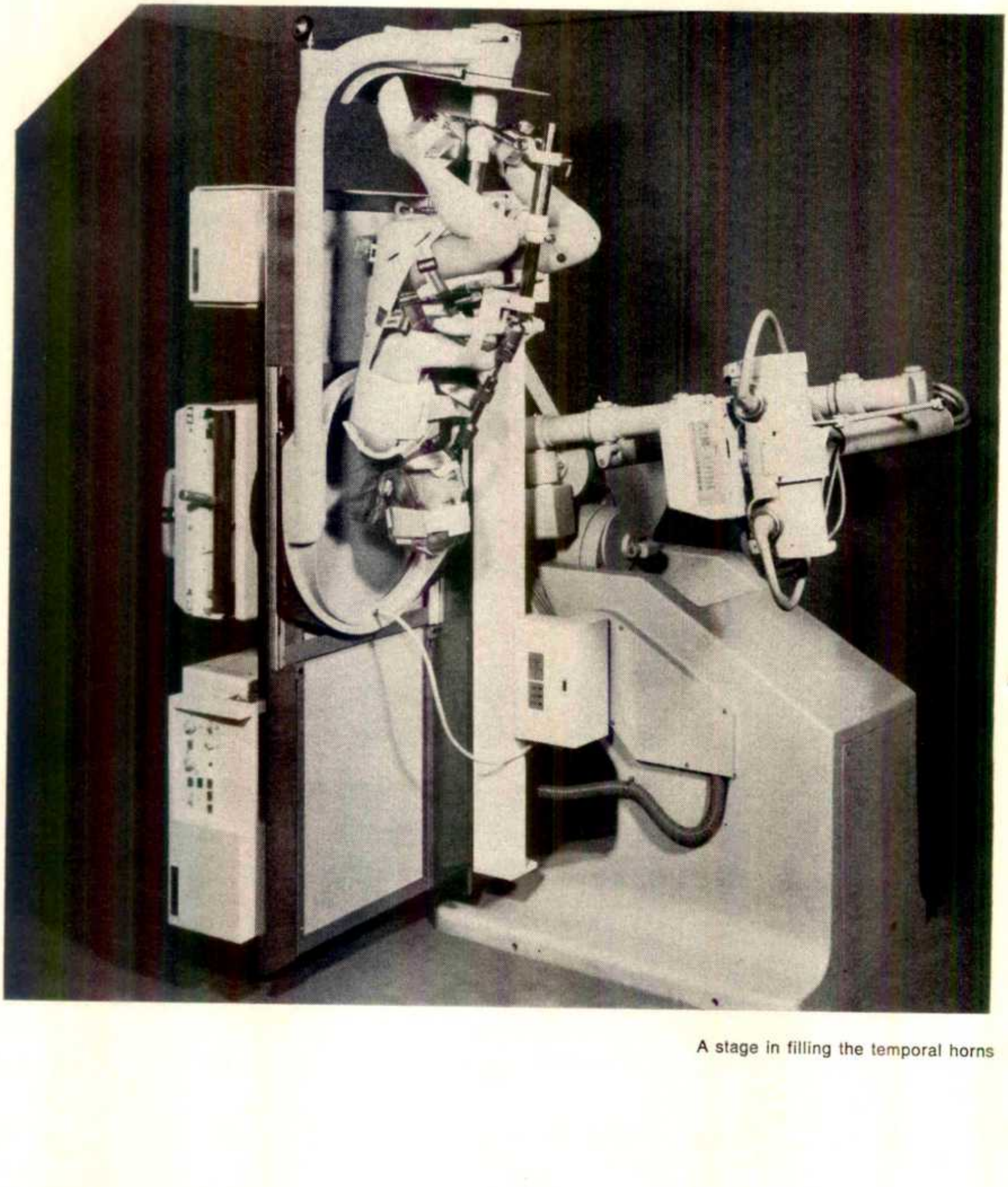

A stage in filling the temporal horns

and Pneumo Chair

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Detach the chair and return the POLYTOME to its role as top department performer !

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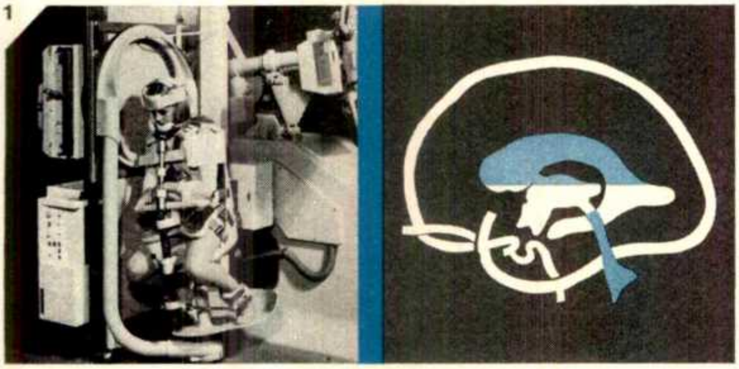

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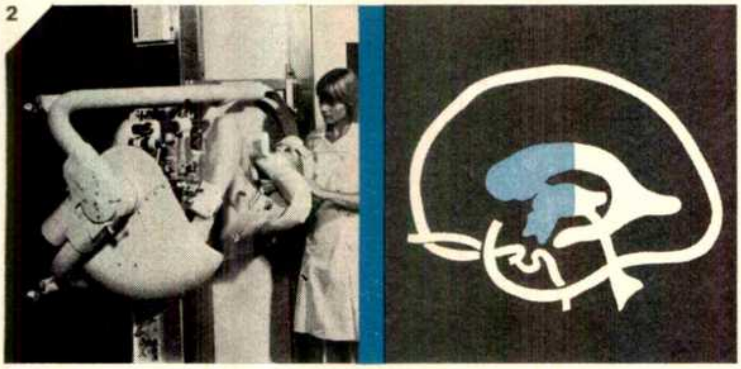

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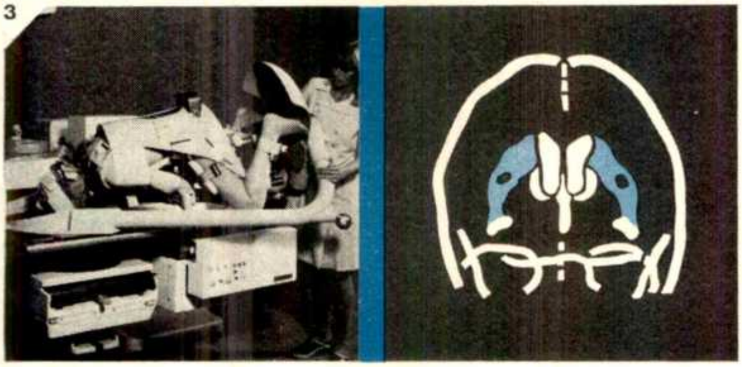

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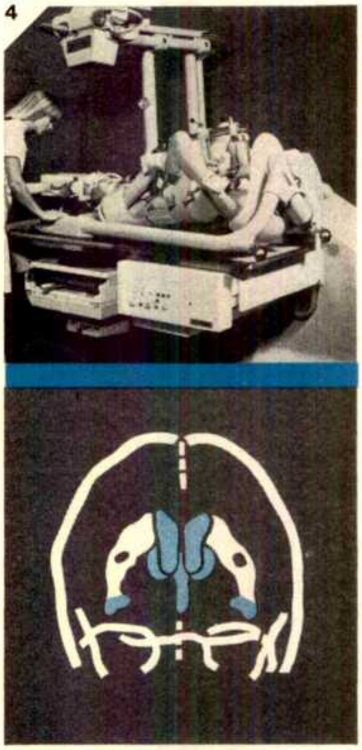

Selected patient positions and visualizations in a common pneumo procedure

1. Erect: lateral
2. Brow-up: lateral
3. Brow-down: PA
4. Brow-up: AP

(After sequential filling of temporal horns)

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Essential: FRCR or equivalent and five years experience in Radiology. Part payment of travelling expenses in certain circumstances.

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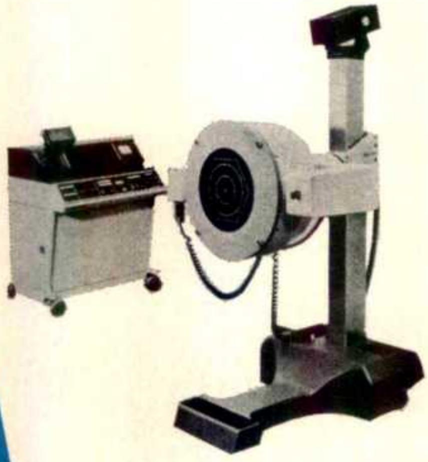

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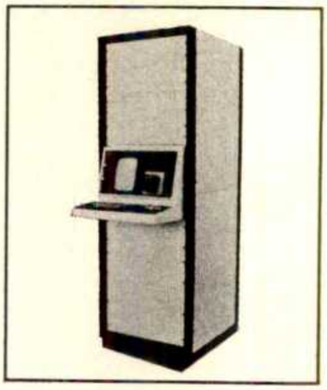

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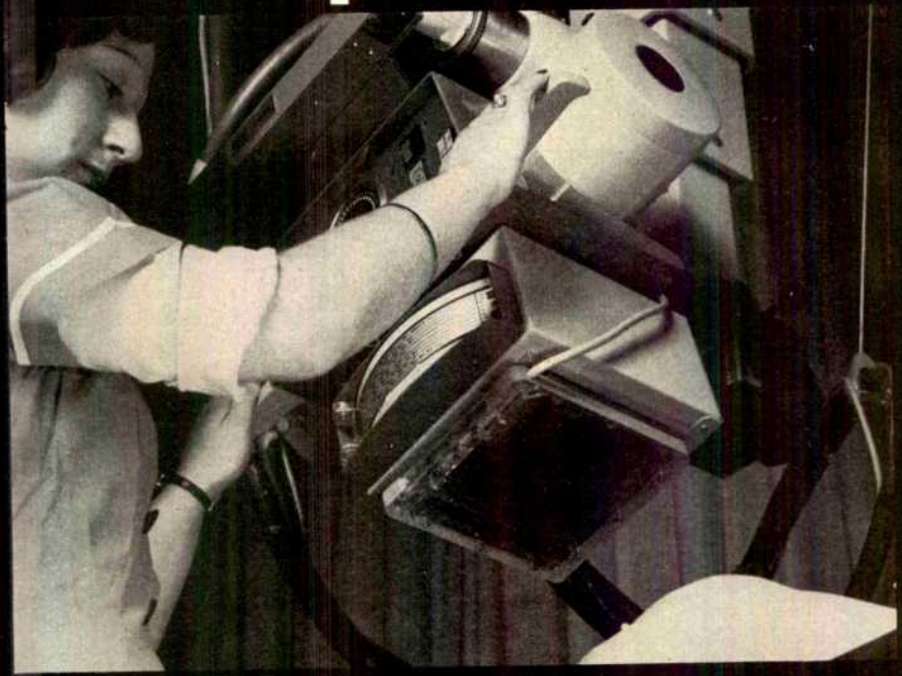

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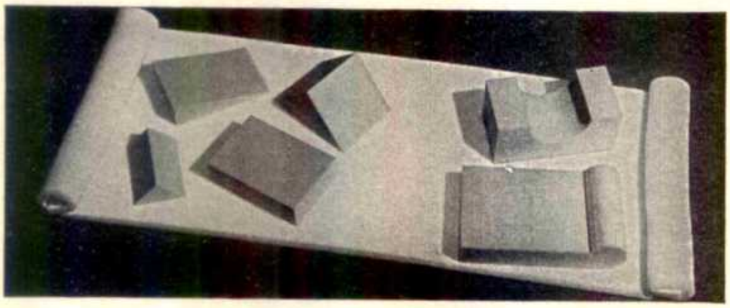

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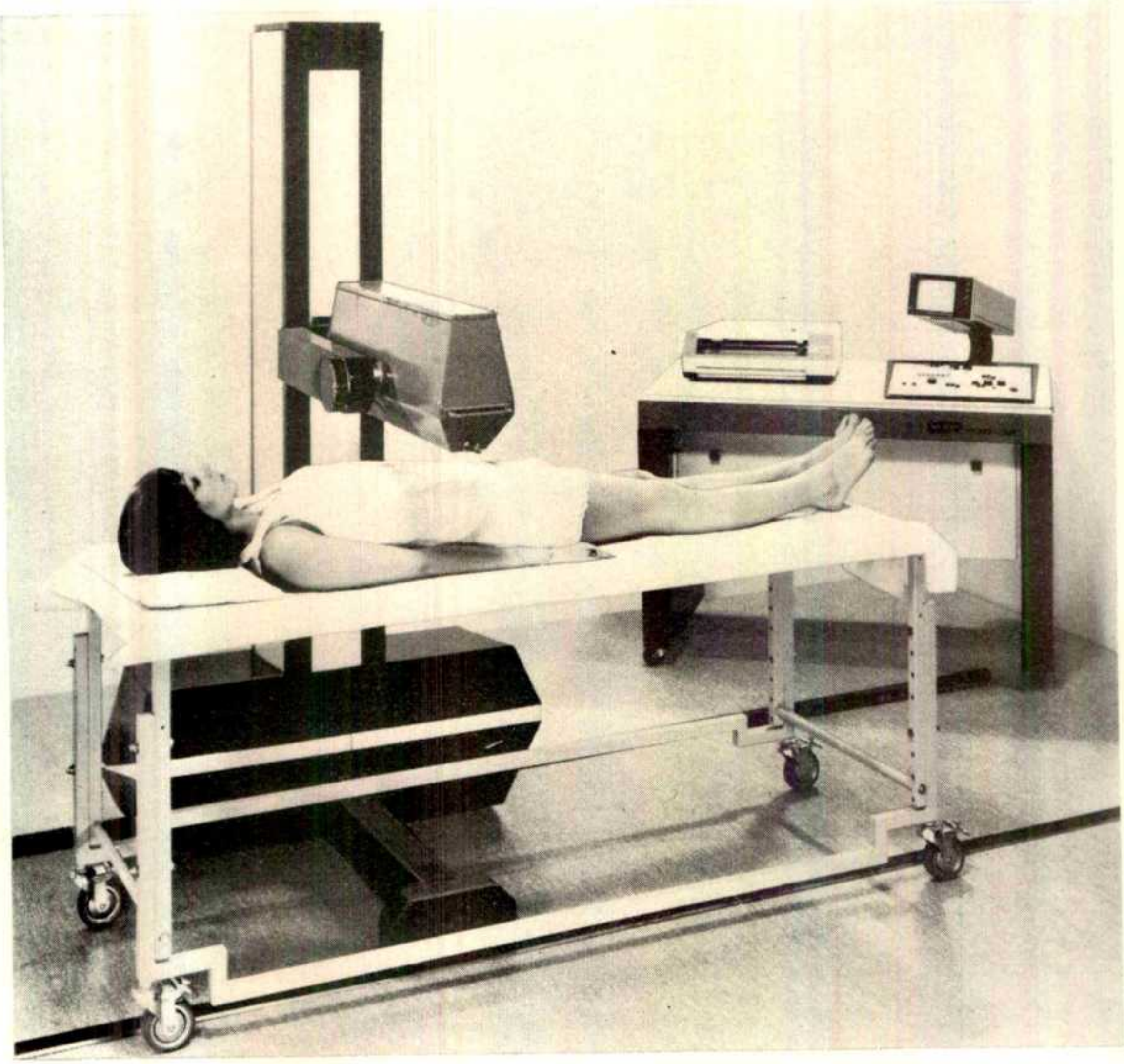

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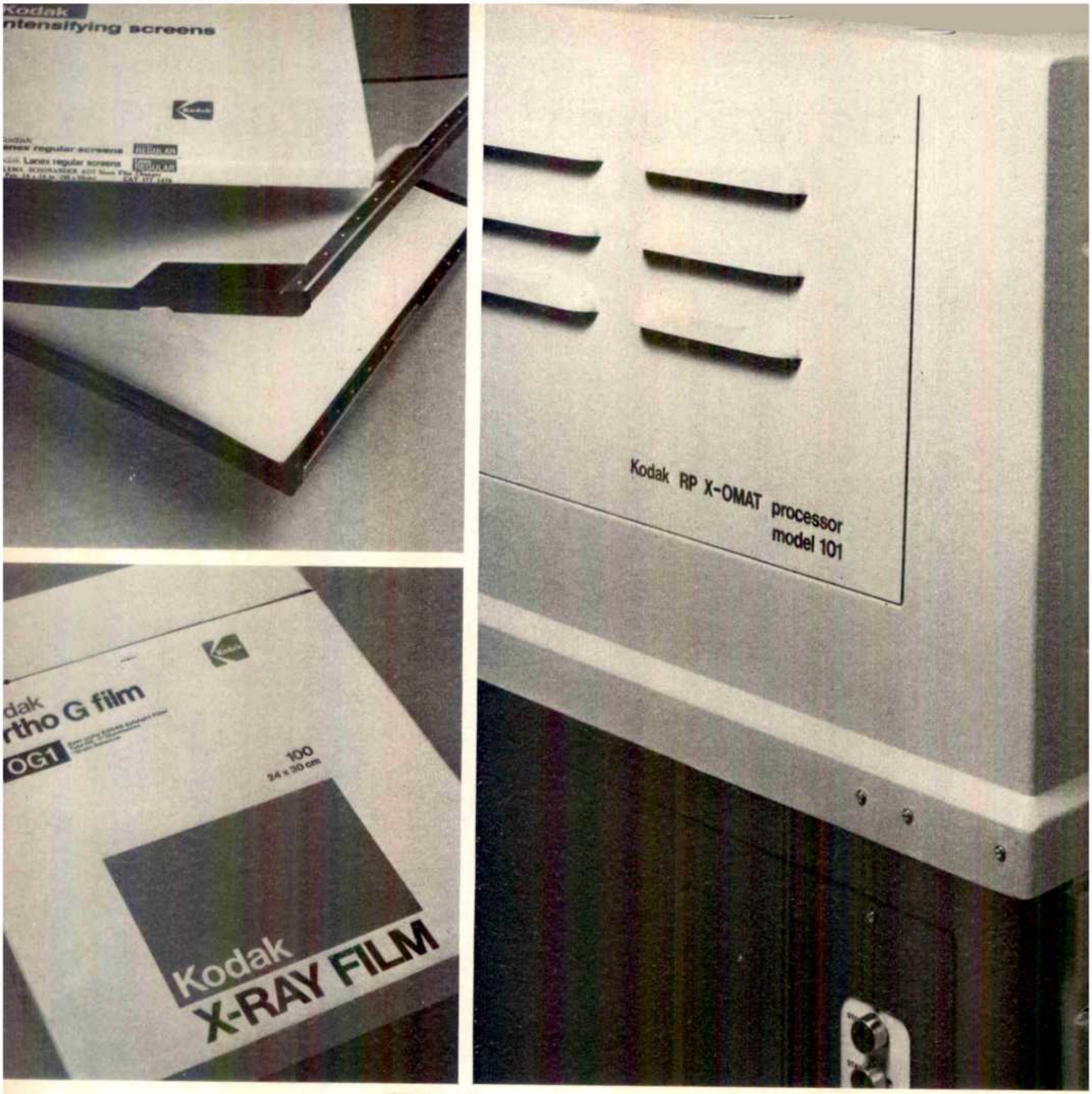

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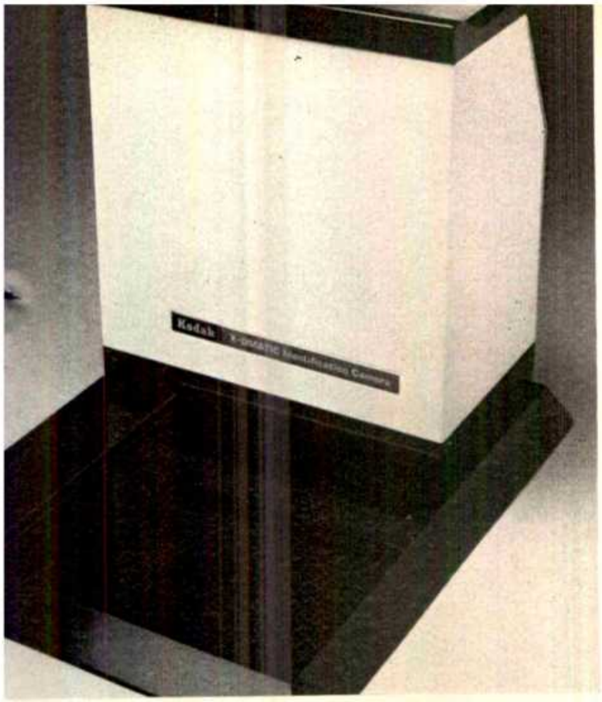

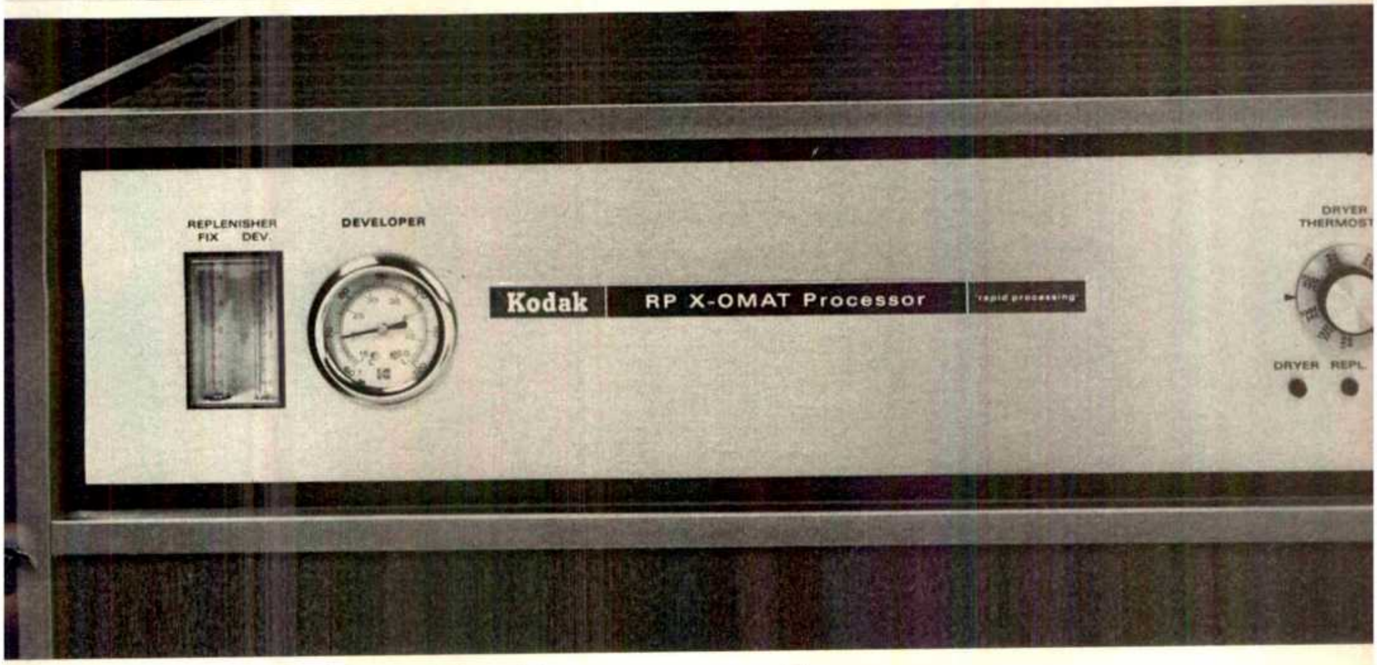

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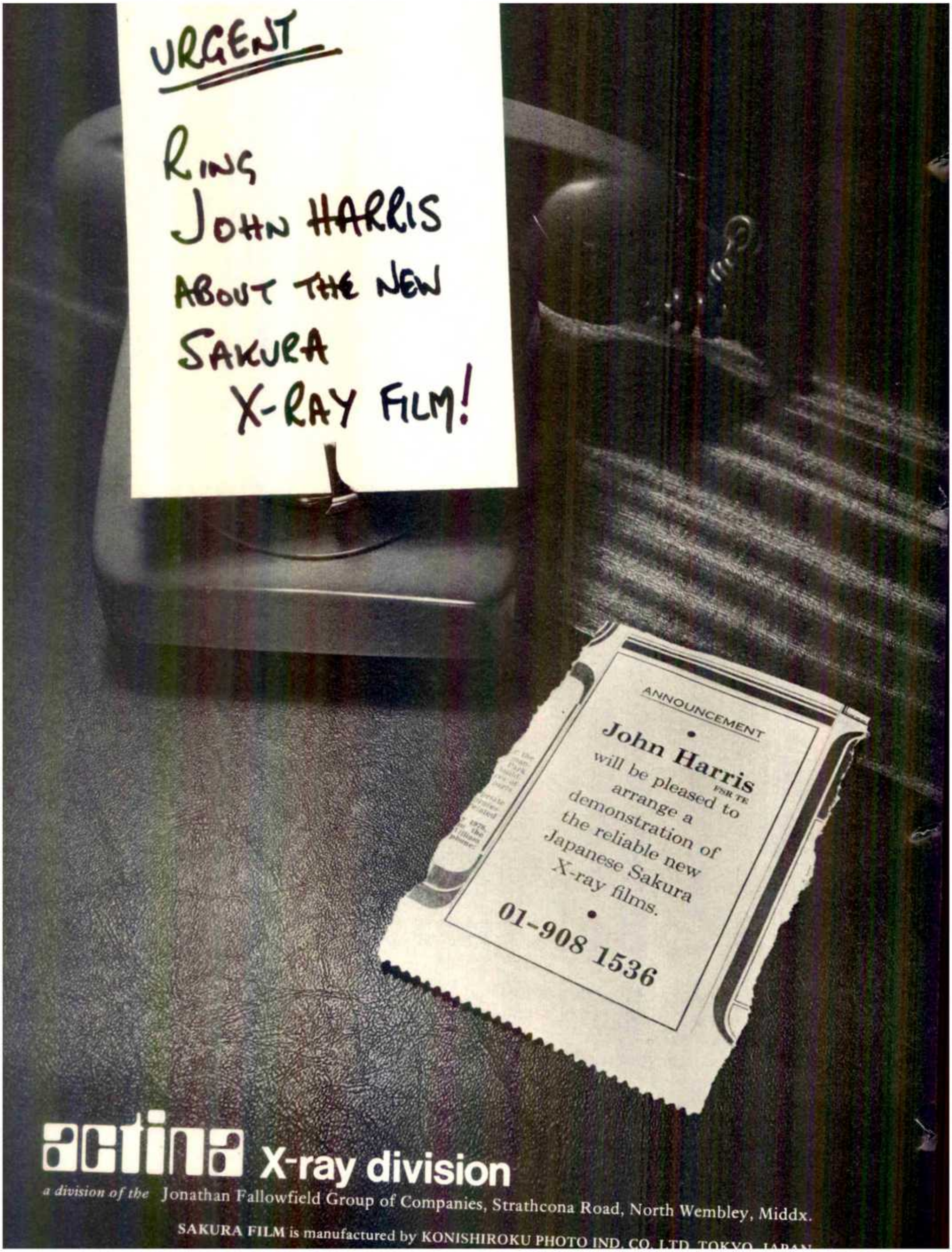

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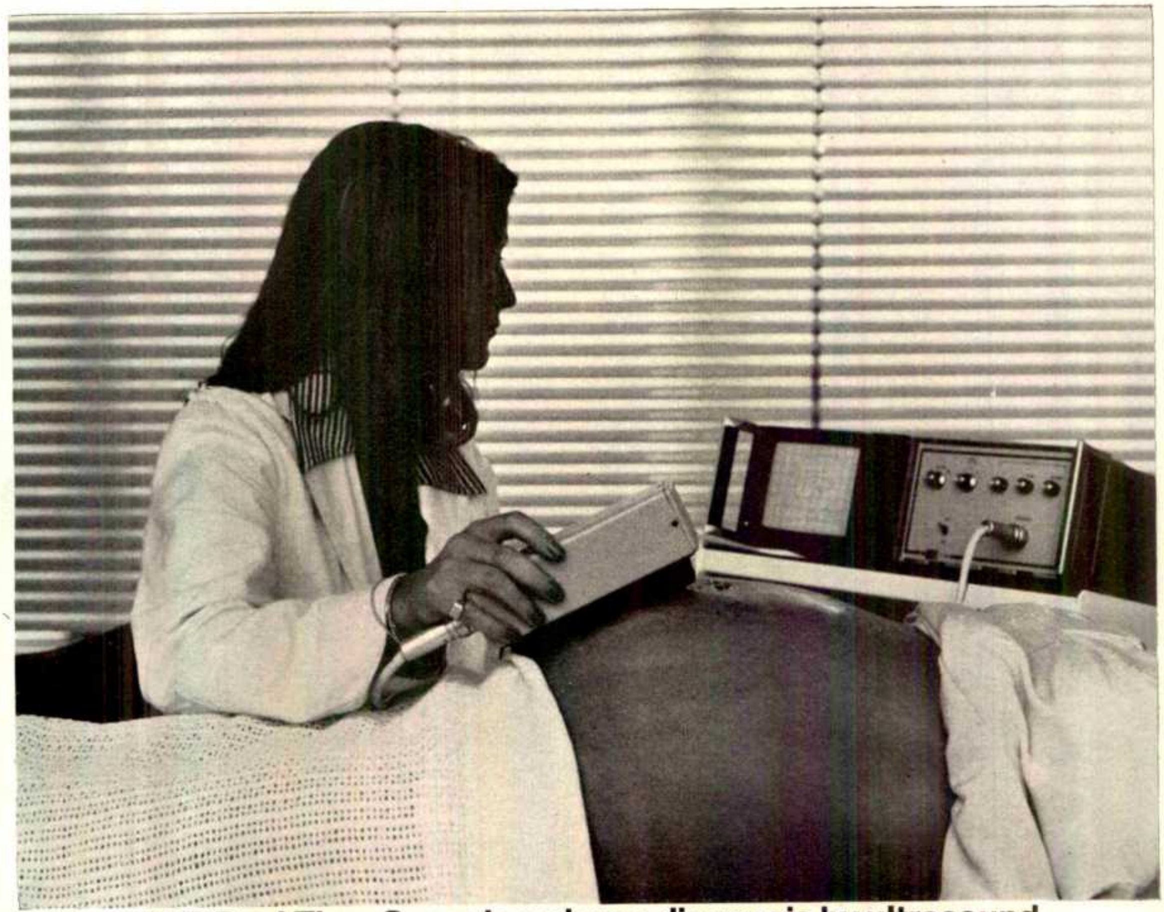

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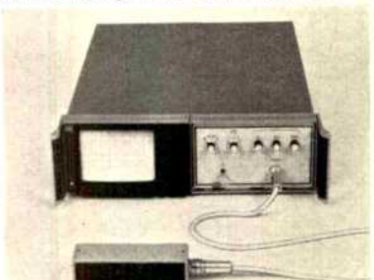

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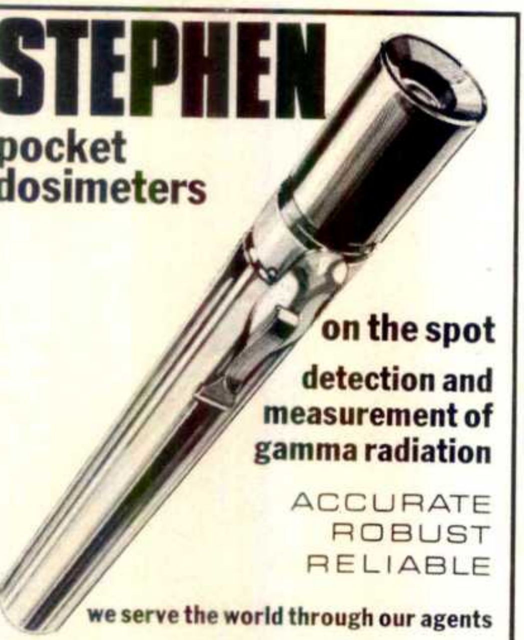

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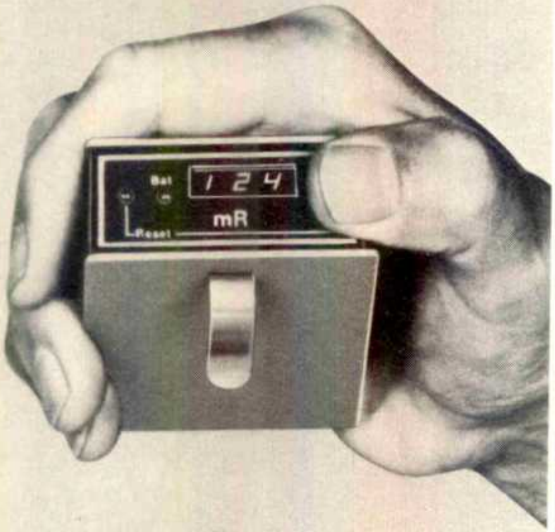

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By Professor C. J. Hodson, T. M. J. Maling, P. J. McManamon and M. G. Lewis

The association between vesico-ureteric reflux and renal damage has been recognized for some time, but it has usually been assumed that the damage is due to infection promoted by the reflux. However, observations by Rolleston and his colleagues in New Zealand have indicated a link between the severity of reflux and renal damage. Furthermore they have suggested that reflux penetrating into the renal substance is the factor most likely to explain the production of renal scarring.

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1977, *British Journal of Radiology*, *50*, 161–163
VOLUME 50 NUMBER 591

MARCH 1977

The British Journal of Radiology

Radiology now

The radiological diagnosis of interstitial pulmonary oedema*

The classical textbook description of pulmonary oedema is that of a patient suffering increasing dyspnoea with episodes of paroxysmal nocturnal orthopnoea and distress. The patient is usually cyanosed or ashen grey in these episodes, during which he may expectorate frothy sputum, sometimes blood-stained. Clinical examination reveals widespread coarse râles and crepitations and radiological examination demonstrates large "cotton-wool" opacities in both lungs.

That is the picture of gross pulmonary alveolar oedema, but it certainly does not represent the earlier stages of a disease process characterized by a pathological increase of fluid in the extravascular lung tissues. "That was the scene that *was*." During the past 20 years, great advances have been made in the evaluation of the pulmonary circulation and of lung water as depicted on the plain radiograph of the chest. The simple conventional *erect* chest radiograph is now appreciated as providing a static pictorial representation of such dynamic functions as pulmonary arterial pressure, pulmonary venous and capillary pressure, and the varying balance of fluid moving into and out of lung tissue. This invaluable information is available because air in the alveoli provides an ideal contrast medium, perfectly positioned to visualize not only the alveolar component, but also the interstitium of the lung and the arteries and veins which carry blood to and from the alveoli. The radiologist has now replaced the physician in the early diagnosis of pulmonary oedema, when the patient may have neither diagnostic clinical signs nor symptoms.

Pulmonary oedema occurs whenever more fluid transudes from the lung capillaries than can be removed by the lung lymphatics. There accumulates therefore an excess of extravascular lung water. The most important factors causing pulmonary oedema are an increase in pulmonary capillary pressure (secondary to an increase in pulmonary venous pressure), and an increase in pulmonary capillary permeability. The former is much the more frequent determining factor, and results from left heart failure of any cause, *e.g.* pulmonary venous obstruction (thrombosis), left atrial failure in mitral stenosis, left ventricular failure in aortic valve disease, hypertension, myocardial infarction, etc. Whenever the pulmonary venous (and therefore the capillary) pressure exceeds the plasma colloid osmotic pressure of 25 mm Hg, then fluid is likely to accumulate in the lung tissues.

All pulmonary oedema fluid begins as a transudate from the capillaries into the alveolar wall, where it may remain or from where it may escape into the adjacent alveolar air spaces. Interstitial pulmonary oedema is therefore a necessary precursor of alveolar oedema. Both patterns of oedema may be acute or chronic: each produces a completely different radiological picture although both frequently co-exist.

INTERSTITIAL PULMONARY OEDEMA

The radiologist is the first person who can make this very important diagnosis and draw attention to a potentially dangerous situation.

The most important radiological sign is the demonstration of "thickening" of the interstitial tissue of the lung. This is a mosaic of delicate connective tissue which forms a continuous lattice work permeating the lung. There is a minute quantity of interstitial tissue surrounding the capillaries in the alveolar walls. Each secondary pulmonary lobule is separated from its neighbours by thin interlobular septa which are continuous with the connective tissue layer lying immediately beneath the visceral pleura. Each bronchovascular bundle and each vein passing through the lung is enclosed in a thin sheath of connective tissue. All of this interstitial tissue is connected together to form a continuous system. Lymphatic vessels run in this interstitial network.

Peter Kerley of Westminster Hospital described lines A, B and C in 1933 and speculated that they might be due to distended lymphatic vessels in the interstitium of the lung. This was an inspired speculation for it was *almost* correct, but subsequent correlation with whole lung sections has conclusively demonstrated that lines A and B are due to interlobular septa or tissue planes which have been thickened by oedema fluid, fibrous tissue, malignant cell invasion, or dust or metal particles. If the alveoli on both sides of the thickened sepata are normally aerated, and if the X-ray beam strikes the septa end-on, then these sheets of connective tissue project characteristic fine-hair lines on the radiograph. These lines are so radio-opaque for their very fine calibre (1 mm) that they cannot possibly be due to structures of (approximately) circular cross-section (either arterial, venous or lymphatic). It is quite incorrect to call them lymphatic lines: they are best called "septal" lines.

---

*Reprints from Dr. R. G. Grainger, Department of Radiology, The Royal Hospital, West Street, Sheffield S1 3SR.

The most frequent cause of lines A and B is interstitial pulmonary oedema, in which the interlobular septa are distended with oedema fluid. The draining lymphatic vessels which are contained within the septa are of course also distended but they account for only about 10% of the septum thickness. Lines A and B occur in both acute and chronic pulmonary oedema, but A lines are much more frequent in oedema of acute onset. The variability and the rapidity of appearance and disappearance of the lines are characteristic features of acute oedema, and are invaluable guides to the degree of left heart failure and its response to treatment. These lines very rarely occur in acute inflammatory lung disease. They are among the most valuable and important radiological signs ever seen on a chest radiograph. Recognition of lines A and B requires not only a high index of suspicion, but also a very critical analytical approach, for their presence is always of major significance in the clinical management of the patient, and it is very important not to over-diagnose them.

The anatomical basis of B lines is the septa separating individual lobules in the most peripheral "layer" of the lung (Grainger, 1958; Fleischner and Riener, 1954). They are 1–2 cm long and when thickened may be seen meeting the costal, diaphragmatic or mediastinal pleura, to which they are always perpendicular. The anatomical basis of the longer more central A lines has been more controversial, but they are now known to be due to thickening of connective tissue sheets or plates (in which lie communicating lymphatics), running medially to link up with the connective tissue sheaths surrounding the bronchovascular bundles and veins near the centre of the lung, usually in the upper lobes (Trapnell, 1973).

Lines C are rarely, if ever, seen in life, and they are best ignored in the clinical context. They are *not* due to the subpleural lymphatic plexus, which is not demonstrated even on the inflated oedematous whole lung removed at autopsy (Kreel *et al.*, 1975).

Kreel *et al.* (1975) have recently drawn attention to intrapulmonary lines other than A, B and C, which may be seen in patients with pulmonary oedema. Kreel *et al.* named them D lines and showed in inflated formalin-fixed lungs removed at autopsy that lines thicker and longer than conventional A and B lines may occur in some patients with pulmonary oedema. These lines usually run backwards from the anterior pleural surface, are 2–4 mm thick, and may be several centimetres long. They are due to oedematous connective tissue sheets which join the connective tissue sheaths surrounding the veins and bronchovascular bundles in the inner third of the lung. The present author can confirm this interpretation, having noted them on Gough paper-mounted lung sections—they are particularly long and thick interlobular septa running backwards from the anterior pleural surface and separating several "layers" of lobules extending towards the hilum. We agree with Kreel that these D lines would have achieved earlier recognition if lateral radiographs were more frequently taken in patients with pulmonary oedema.

Less valuable radiological signs of interstitial pulmonary oedema are pleural oedema, peribronchial and perivascular cuffing, and hilar haze.

As subpleural connective tissue is a continuum of the interstitial tissues of the lung, subpleural oedema is a manifestation of interstitial pulmonary oedema. Subpleural oedema causes thickening and increased visibility of the interlobar fissures, and of the costal pleura at the costo-phrenic sulcus.

Peribronchial and perivascular cuffing is due to oedema of the connective tissue which surrounds the bronchi and vessels in the lung. A bronchus seen end-on near the hilum becomes surrounded by a cuff of a thickened radio-opaque band; the vessels, seen either end-on or longitudinally appear a little greater in calibre and may have a slightly blurred outline. Hilar haze is an ill-defined loss of the normal radiolucency of the lung about the hilum. These latter radiological signs are difficult to assess on a single radiograph and may only be confirmed by comparing sequential films.

Redistribution of blood flow from the lung bases to the upper zones is a very frequent accompaniment of pulmonary oedema due to left heart failure. Interstitial pulmonary oedema is a significant causative factor of redistribution in failure, when basal pericapillary oedema tends to increase peripheral resistance to blood flow through the lung bases. Blood flow is thus diverted from the normal predominantly lower zone distribution to the upper zones where empty capillaries are waiting to be recruited to the active circulation.

In the erect healthy patient, the upper third of the lungs receives very little blood flow (and upper zone vessels are very small on the radiograph) as the pressure generated by the right ventricle is barely adequate to pump blood against gravity. Redistribution of blood flow is recognized by the dilatation of the vessels to the upper zones, and the narrowing of the vessels to the lower zones. This valuable radiological sign can only be used to diagnose pathological redistribution of pulmonary blood flow on an *erect* chest radiograph, for the same redistribution occurs as a physiological phenomenon when a healthy patient lies down, and thereby negates the effect of gravity on pulmonary blood flow.

Pre-existing lung disease may considerably alter the pathological and therefore the radiological distribution of pulmonary oedema fluid. Areas of lung (*e.g.* emphysema) which have lost their capillary bed, or are not perfused because of pre-existing disease, cannot become oedematous, nor can blood flow be diverted to them.

In the past two decades, the radiologist has become much more aware of cardiovascular physiology and the way it becomes disturbed in disease processes. An excellent review is presented by Milne (1973) which is strongly recommended reading. We now appreciate the erect chest radiograph as a sensitive manometer of pulmonary venous (and capillary) pressure, and we have learnt to recognize the important signs and the significance of redistribution of pulmonary blood flow. The radiological diagnosis of interstitial pulmonary oedema is now on a more substantive basis, carefully correlated with anatomical and physiological parameters and confirmed by autopsy radiology and histology.

To the radiologist is accorded the opportunity and the responsibility of first suggesting the diagnosis of pulmonary oedema, with the frequent serious implication of failure of the left heart.

RONALD G. GRAINGER.

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Review article

Gastro-oesophageal reflux, hiatus hernia and the radiologist, with special reference to children

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ABSTRACT

Gastro-oesophageal reflux can lead to peptic oesophagitis and stricture formation. This is particularly true in infants in whom the condition should be suspected if the patient presents with vomiting, anaemia and failure to thrive. The anatomy of the oesophago-gastric junction is described. The inferior oesophageal sphincter is the main barrier to reflux, and marks the functional junction between oesophagus and stomach. It is under nervous and hormonal control. It is weak in the neonate who therefore frequently refluxes. An hiatus hernia can cause problems due to its bulk but the main problem of peptic oesophagitis is due to gastro-oesophageal reflux. The radiological examination should be carried out carefully with the patient swallowing in a prone position. The patient should be put in the Trendenlenberg position and compression applied to the abdomen. Reflux is intermittent and a negative examination should be repeated if the clinical findings suggest a diagnosis of peptic oesophagitis. Associated pyloric stenosis should always be excluded. Radiological examination of the gastro-oesophageal junction remains the quickest, simplest, and most convenient and safe technique as long as its limitations are appreciated.

The function of the gastro-oesophageal area can be assessed by means such as intraluminal pH and pressure measurements, radioisotope assessment of reflux or by endoscopy, and it is possible to write a good review of the subject with barely a mention of radiology (Pope, 1976). However, radiologists are frequently asked to assess the gastro-oesophageal junction, to record the presence of gastro-oesophageal reflux, of hiatus hernia, and to comment on their findings. To a large extent these depend on the examining technique, and their interpretation depends on the radiologists' view of normal and abnormal anatomy and physiology of this region. Although these have not yet been completely elucidated the radiologist can, with our present knowledge, pinpoint abnormalities in the gastro-oesophageal region, and assess whether they are related to the patient's symptoms and signs. A knowledge of anatomy, physiology and clinical signs is needed.

ANATOMY

The anatomy of the gastro-oesophageal region is shown diagrammatically in Figs. 1 and 2. The oesophagus passes through the diaphragm at the hiatus. This level can be defined manometrically as the level at which the negative intrathoracic pressure (−3 mm Hg to −8 mm Hg) changes to the positive intra-abdominal pressure (2 mm Hg to 7 mm Hg). Radiologically it is the level at which the medial borders of the leaves of the diaphragm are assessed to meet on a straight film. The hiatus moves with

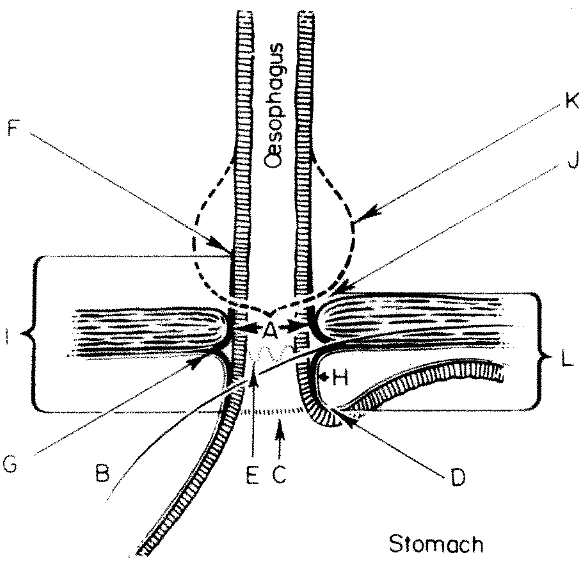

FIG. 1.

Reprinted (by permission of Editor of *Paediatric Gastroenterology*) from Charlotte Anderson and Valerie Burke. *Diagrammatic representation of gastro-oesophageal region*

A Hiatus formed by diaphragmatic crura
B Position of diaphragm as portrayed by conventional radiography
C Site of gastro-oesophageal junction
D Cardiac incisura (site of attachment of sling fibres)
E Irregular interdigitating junction of squamous and junctional columnar epithelium (Z line)
F Upper limit of attachment of phreno-oesophageal ligament (G)
H Peritoneum
I Gastro-oesophageal sphincter and manometric high pressure zone
J Site of "physiological" hiatus, *i.e.* manometric pressure inversion point
K Epiphrenic ampulla
L Intra-abdominal portion of oesophagus, *i.e.* radiologically defined empty segment.

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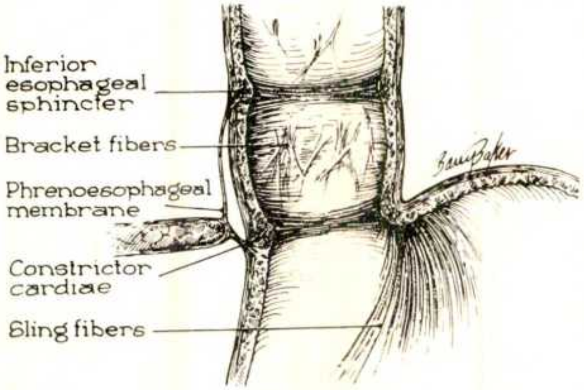


FIG. 2.

Diagrammatic representation of muscular structures at oesophago-gastric junction. (Reproduced with kind permission of Editor of *New England Journal of Medicine*, from article by Goyal *et al.*, 1971.)

respiration. The oesophagus is held in place by the phreno-oesophageal ligament (Muller-Botha, 1958; Friedland *et al.*, 1966). In infancy this is a strong membrane containing elastic and collagen fibres. It becomes less prominent and weaker with age, and this fact is used to explain the increased incidence of hiatus hernia in the old. It is apparently a prominent structure when the anatomy is normal, but becomes difficult to identify when distorted by an hiatus hernia.

In the adult there are about 3 cm of subdiaphragmatic intra-abdominal oesophagus before reaching the stomach. This portion is very short in infants. The adult oesophagus joins the stomach at the cardia where it forms an acute angle with the stomach—the incisura. This angle is either absent or much less acute in infants, in whom the oesophagus and stomach tend to form a continuous straight tube. The mucosa of the oesophagus is squamous epithelium while gastric mucosa is columnar. The change-over takes place at the "Z line". This is usually a very irregular demarcation line, except in 10% of patients in whom it is straight, and thought to be the cause of a narrow oesophageal ring, which is only seen when the oesophagus is full of barium (Schatzki ring) (Fig. 3) (Goyal *et al.*, 1970). The position of the Z line in the remaining 90% of patients cannot be identified radiologically. The columnar mucosa in the area adjacent to the Z line forms a transition zone devoid of oxyntic and peptic glands but containing mucus secreting glands. Although the Z line in the majority of patients lies within the hiatus its position can vary greatly, and cannot be taken to be the level of the oesophago-gastric junction.

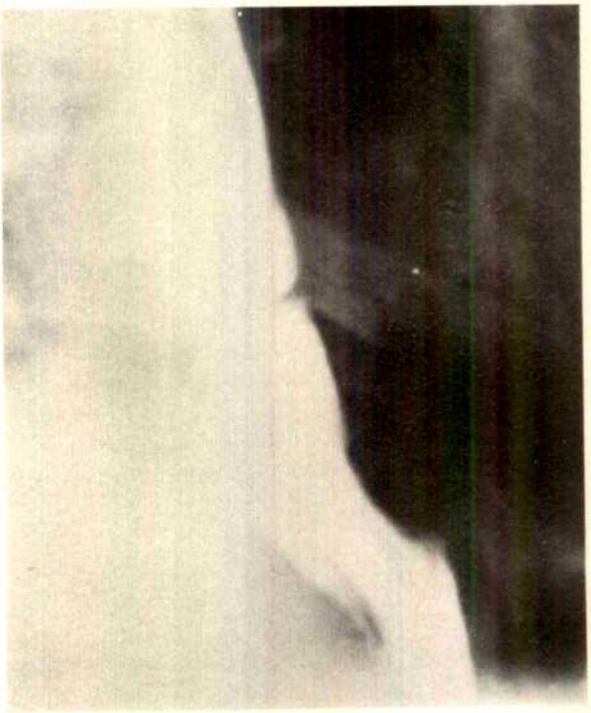


FIG. 3.

The ring at distal end of oesophagus "Schatzki ring". According to Schatzki (1963) and Goyal *et al.* (1971) this marks the squamo-columnar mucosal junction. According to Friedland *et al.* (1966) it is formed by the transverse mucosal fold which on the left side is adjacent to the sling fibres of the stomach. No other clinical or radiological evidence of hiatus hernia or reflux in this patient.

Independent of its epithelium, the oesophageal mucosa is always attached to form longitudinal parallel folds that terminate distally at a definite level, representing the oesophago-gastric junction (Friedland *et al.*, 1966). This level is not necessarily related to the mucosal Z line. The gastric mucosal folds are more numerous, mobile and irregular and radiate away from this level (Fig. 7). The distal oesophageal folds are redundant and help block off the lumen when the inferior oesophageal sphincter contracts, thus forming the "mucosal choke" (Chrispin and Friedland, 1967).

Landmarks at the oesophago-gastric junction

Figure 1 is a diagram of the functional structures at the oesophago-gastric junction as they affect a barium swallow. Figure 2 is a diagram of the anatomy as displayed by dissection. Unfortunately, they do not correlate completely, and the radiologist is not sometimes in doubt about the cause and significance of his findings in this area.

Sling fibres of the stomach

These form the incisura as they loop around the gullet and return to be inserted into the lesser curve of the stomach (Fig. 2).

Inferior oesophageal sphincter and constrictor cardiae

These narrow muscle fibres in Fig. 2 are not represented in Fig. 1, and cannot be seen radiologically. Indeed the functional inferior oesophageal sphincter (Fig. 1, I) is a wide structure usually straddling the hiatus.

Transverse mucosal fold (Friedland *et al.*, 1966)

This fold is said by these authors to overlie the constrictor cardiae muscle (Fig. 2) and to be at the level of the sling fibres on the left side of the gullet. Its level is therefore the oesophago-gastric junction. These authors state that the transverse mucosal fold is not related to the Z line. This fold is in the differential diagnosis of a lower oesophageal ring (see below).

PHYSIOLOGY

The inferior oesophageal sphincter or high pressure zone is the functional junction between the oesophagus and stomach, and its level is used radiologically and manometrically to diagnose a hiatus hernia or intrathoracic stomach (Carré and Astley, 1958). It appears to correspond to the "vestibule" mentioned by many writers, and it is approximately 3 cm long (Figs. 1, 4, 5). Although Carré and Astley found that the inferior oesophageal sphincter was intrathoracic in infants with an hiatus hernia, and within the hiatus in the normals, other investigators (Strawczinski *et al.*, 1964) found it above the hiatus in 70–80% of normal and abnormal infants, while it was straddling the hiatus in 15 normal adults. The normal pressure of the inferior oesophageal sphincter is 15–30 mm Hg above gastric pressure (Carré, 1975). Strawczinski *et al.* (1964) found that the inferior oesophageal sphincter had a low tone in the first two weeks of life but attained adult pressures by one month.

The inferior oesophageal sphincter is under neural (vagal) control and will relax when the patient goes through the act of swallowing, even though nothing passes down the gullet (Chrispin and Friedland, 1966; Gryboski *et al.*, 1963). It is also under hormonal control; an increase in serum gastrin increases tone, as will parasympathomimetic drugs such as bethanechol, or cholinesterase inhibitors such as edrophonium hydrochloride (Lipshutz *et al.*, 1973; McCall *et al.*, 1975). An increase in intra-abdominal pressure will increase the pressure in the inferior oesophagel sphincter whether the sphincter is intra-abdominal or intra-thoracic as in an hiatus hernia (Cohen and Harris, 1969).

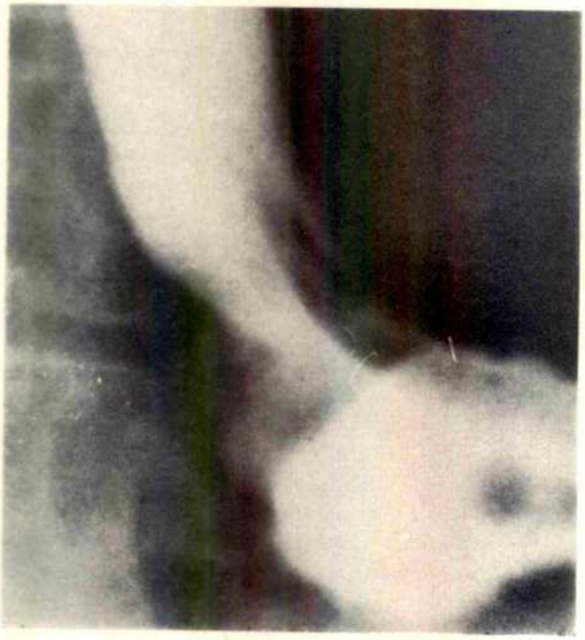


FIG. 4.
Inferior oesophageal sphincter ("vestibule") open.

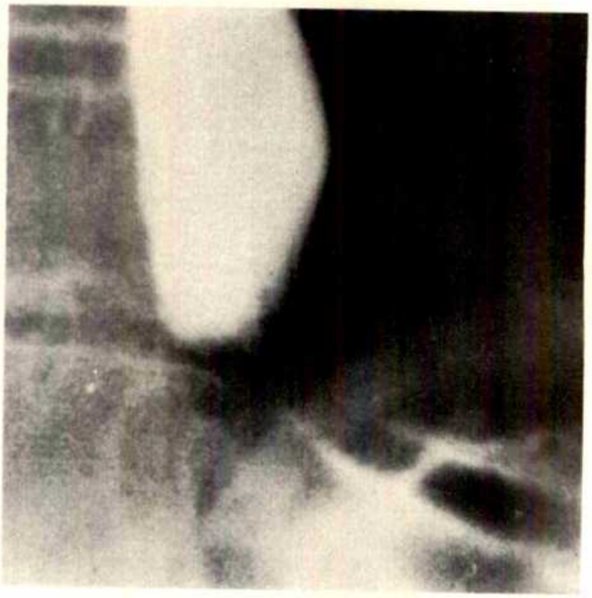


FIG. 5.
Inferior oesophageal sphincter ("vestibule") shut.

MECHANISM OF THE OESOPHAGO-GASTRIC JUNCTION

This is a controversial subject that has not yet been completely settled. However, some theories can now be discounted, such as the valvular action of the incisura, or the pinch-cock theory that postulated that the crura of the diaphragm act as a sphincter to close off the distal oesophagus at the hiatus. (However, as a radiologist looking at the TV monitor and the films one would still like to give the diaphragmatic pinch-cock some function.)

VALVULAR ACTION OF THE INTRA-ABDOMINAL OESOPHAGUS (FLUTTER VALVE THEORY)

This postulates that the high intra-abdominal pressure acts on the oesophagus in the abdomen at the level of the mucosal choke and closes it off (Milstein *et al.*, 1961). The effect is potentiated by the negative intra-thoracic pressure which exerts a sucking force on the closed oesophagus, and thereby tends to close it off even further, since suction on a flutter valve closes it. This theory ignores the fact that the zone of intraluminal high pressure (*i.e.* the zone of the inferior oesophageal sphincter) lies within the intra-abdominal oesophagus, and that this pressure would therefore tend to open the oesophagus if it were acting as a flutter valve. It is also difficult to understand how this explanation accounts for hiatus hernia without reflux, when the oesophago-gastric junction is surrounded by the low intra-thoracic pressure. Also the intra-abdominal oesophagus in infants is very short and cannot act as a flutter valve. However, this mechanism will explain the holdup of barium in the oesophagus during inspiration and its emptying on expiration.

THE INFERIOR OESOPHAGEAL SPHINCTER MECHANISM

Although difficult to identify histologically (Muller-Botha, 1958; Friedland *et al.*, 1966), the presence of this sphincter or high pressure zone at the distal end of the oesophagus has been amply confirmed (Carré and Astley, 1958; Cohen and Harris, 1969, and many others). The sphincter has been shown to be strong enough to prevent reflux even in the presence of an hiatus hernia when it lies within the thorax (Cohen and Harris, 1969). The neural and hormonal control of this sphincter have already been mentioned. Patients with reflux have been shown to have a reduced sphincter pressure and their sphincter responds poorly to gastrin. Lipshutz *et al.*, 1973; Behar *et al.*, 1975, and Lipshutz *et al.*, 1974, found that the resting inferior oesophageal sphincter pressure became nearly normal after successful operation. The operations surveyed by these authors consisted of reduction of the hiatus hernia, fundoplication and fixation of the stomach in the abdomen to the diaphragm (Hill and Belsey Mark IV procedures).

Although it is possible to improve the inferior oesophageal sphincter pressure within the thorax most operations in the past were designed only to fix the stomach in the abdomen and repair the hiatus (Allison procedure). More recently it has become the custom to add a gastric fundoplication in which the gastric fundus is wrapped around the distal oesophagus (Nissen procedure). The individual variations on these basic operations, the thoroughness and length of the follow-up procedures are very variable, and opposing views on the efficacy of the operations are held (Allison, 1973; Borrie, 1967; Behar *et al.*, 1975; Cahill *et al.*, 1969; Davie, 1975; Hoffman and Sumner, 1973; Lari and Lister, 1972; Lipshutz *et al.*, 1974; Pearson and Gray, 1967; Jewett and Waterston, 1975), but the impression gleaned is that the patient's clinical symptoms are relieved in 70–80% of cases regardless of the type of operation, even though there may be radiological recurrence of the hernia in 40–50%. Allison states that the radiological recurrence of the hernia is not related to the patient's symptoms.

The best explanation to fit these facts is that the fibres of the inferior oesophageal sphincter in a patient with reflux are unable to respond adequately. By placing the sphincter into the high pressure zone of the abdomen and then further supporting the fibres with a fundal plication, one allows them to shorten and regain their proper basal tone (Lipshutz *et al.*, 1974; Behar *et al.*, 1975; Biancani *et al.*, 1975), and thus prevent reflux. If the hernia now recurs the sphincter does not necessarily have to give way again. The situation would be analogous to the infants in whom the hernia persists but reflux ceases (see below).

DEFINITION OF HIATUS HERNIA AND GASTRO-OESOPHAGEAL REFLUX

An hiatus hernia is present when part of the stomach has passed through the diaphragmatic hiatus to lie above the diaphragm. If the incisura is maintained a rolling hiatus hernia is said to be present and the diagnosis is easy (Fig. 6). If the incisura is absent the oesophagus and stomach form a straight tube, and a sliding hiatus hernia is present which may be difficult to diagnose (Fig. 7). The diagnosis then depends on the position of the oesophago-gastric junction as indicated by the position of the inferior oesophageal sphincter, and to a lesser extent on the demonstration of gastric mucosa within the

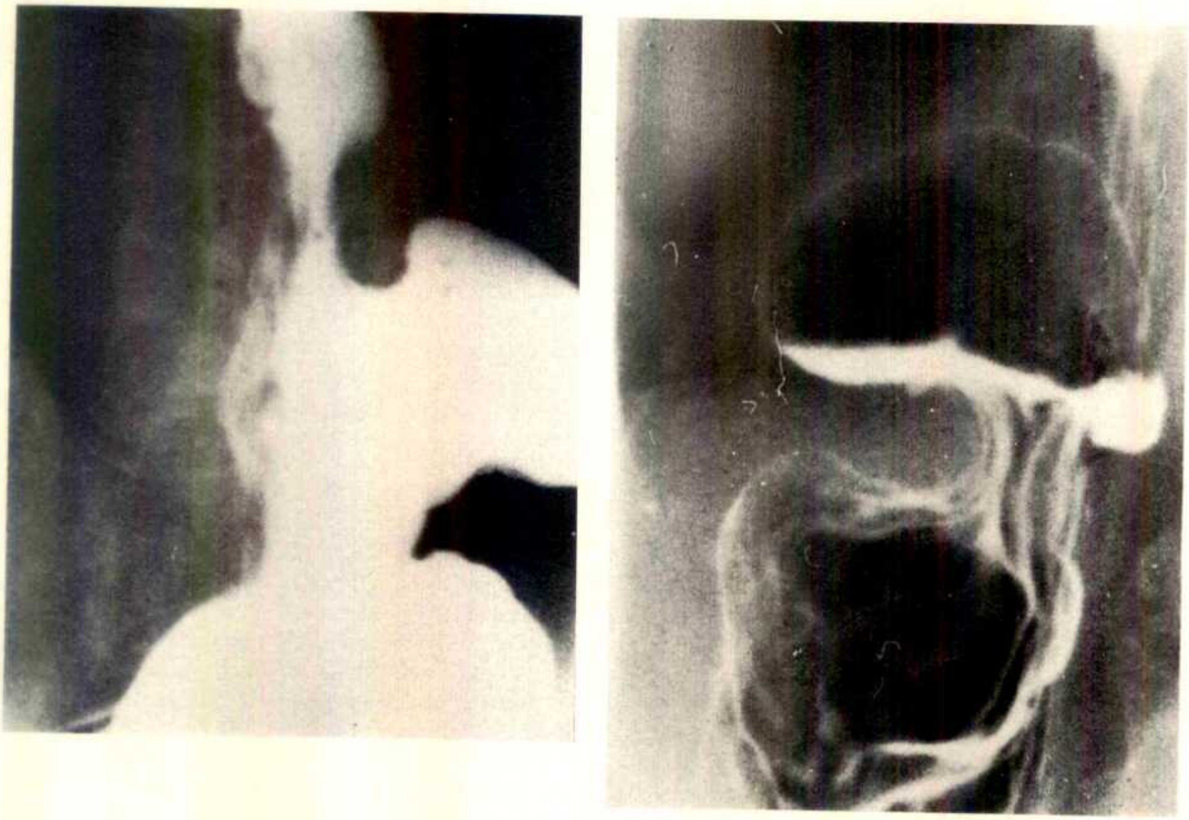
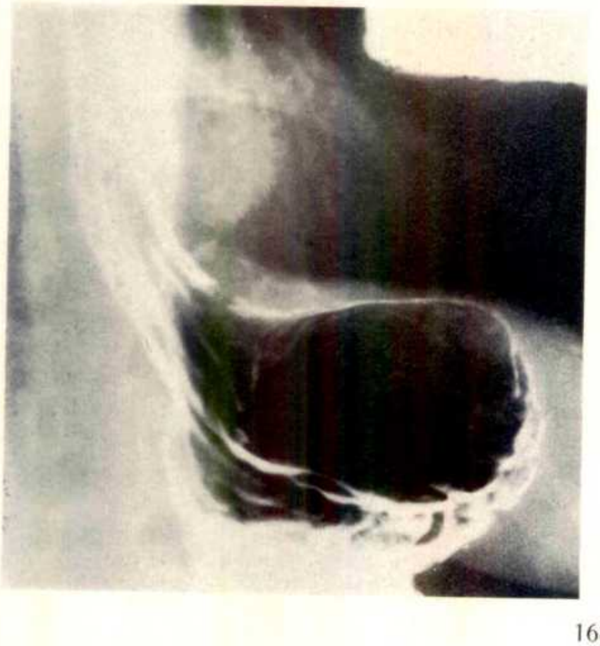


FIG. 6.

Rolling hiatus hernia—incisura present. Note narrowing of stomach as it passes through the hiatus, ? pinch-cock action of crura (A)—supine head down. (B)—erect.



thorax (Fig. 7). It does not depend on the position of the Z line, though in most patients this coincides with the inferior oesophageal sphincter.

Gastro-oesophageal reflux occurs when stomach contents reflux into the oesophagus, *i.e.* above the inferior oesophageal sphincter. Although the phrase "sliding hiatus hernia with reflux" comes easily, it is by no means certain that they are causally related. Two thirds of the infants reported by Carré and Astley (1960) to have lost the symptoms due to reflux and thoracic stomach (hiatus hernia) were found to have a persistent thoracic stomach at follow-up but no reflux. The cure must have been due to some factor not related to the hiatus hernia. Out of 60 "normal" adult volunteers 22 were found

FIG. 7.

Sliding hiatus hernia gastric mucosal folds converging to inferior oesophageal sphincter above diaphragm. Very wide hiatus.

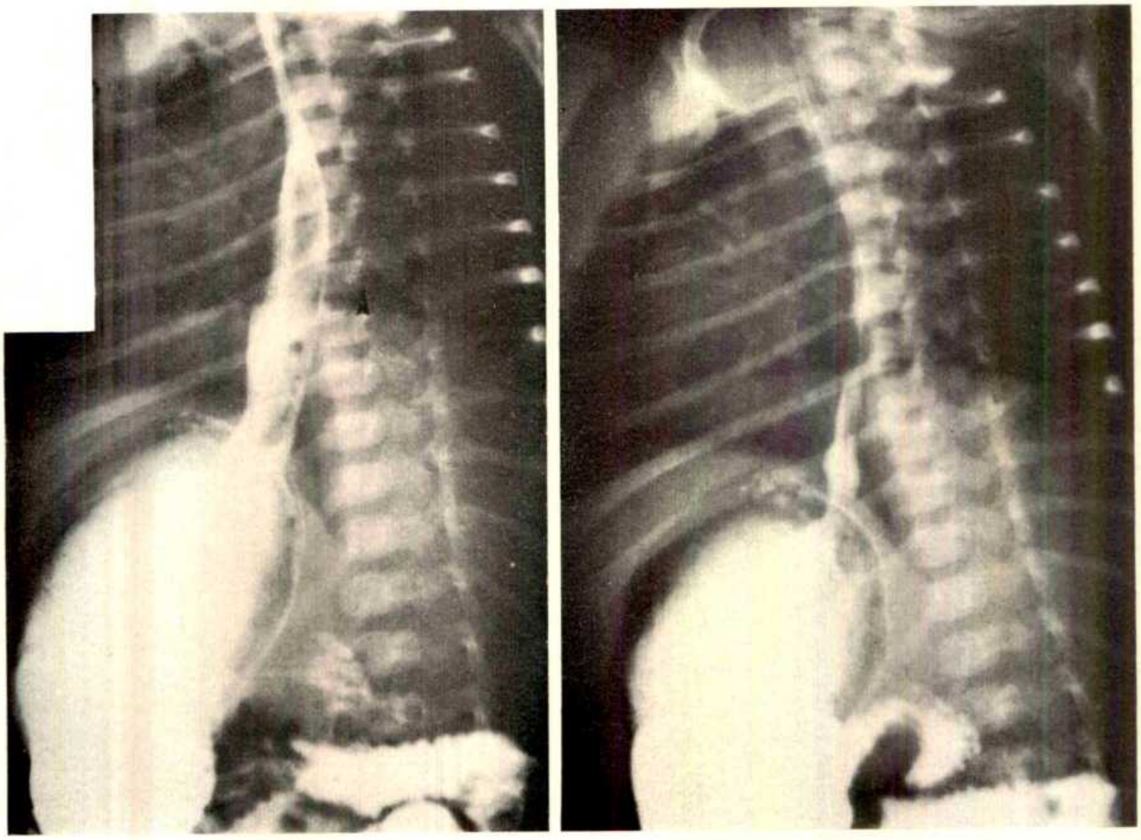


FIG. 8.

(A) Chalasia—reflux but no hernia visible.
(B) Inferior oesophageal sphincter seen below the diaphragm.

to have a radiologically evident hiatus hernia (Venkatachalam *et al.*, 1972), but only four had gastro-oesophageal reflux. Cohen and Harris (1969) flatly state that the presence of an hiatus hernia does not affect inferior oesophageal sphincter competence.

However, in my experience the proportion of patients with significant reflux but no hiatus hernia is relatively small. Neuhauser and Berenberg (1947) reported cases of reflux without hernia and called the condition "chalasia" of the cardia (Fig. 8). Carré (1969) reported 16 cases of reflux without hernia, but found that 13 of these had diagnosable hernias on re-examination, and supposed these had been previously present but not demonstrated.

Therefore, though the discovery of an hiatus hernia does not necessarily denote disease (Dyer and Pridie, 1968), the presence of the hernia should bring the possibility of reflux and oesophagitis to mind. However, the possibility of reflux without hernia should not be forgotten, nor the fact that reflux can be intermittent and may need several examinations for its demonstration.

CLINICAL FINDINGS

Symptoms of gastro-oesophageal reflux and hiatus hernia (Table I)

Except for the rolling hiatus hernia in which the sheer bulk of the lesion can cause respiratory difficulty, the signs and symptoms are those of oesophagitis.

The adult patient is usually obese and complains of flatulence, heartburn, or epigastric pain. Anaemia may be present, and there may be associated haematemesis and melaena (Allison, 1973).

Dysphagia may be present due to an oesophageal stricture (Craig, 1966). This can lead to malnutrition and the mistaken diagnosis of carcinoma of the oesophagus. Peptic ulcers may occur in the oesophagus.

TABLE I

MAIN RADIOLOGICAL AND CLINICAL FINDINGS AND DIFFERENCES BETWEEN INFANTS AND ADULTS SUFFERING FROM REFLUX OESOPHAGITIS AND HIATUS HERNIA

	Infant	Adult
Intra-abdominal Oesophagus	Very short	Well marked
Incisura	Poorly defined	Well defined
Lower oesophageal Rings and notches	Not seen	Seen
Oesophagitis	Seen radiographically	Not seen radiographically
Associated with	Pyloric stenosis Mental retardation	Peptic ulceration Gall bladder disease
Presentation	Failure to thrive (small thin patient) Dysphagia Anaemia Vomiting Chest infections	Heartburn (big fat patient) Dysphagia Anaemia
Prognosis	Over 90% below the age of one improve on medical treatment alone	Medical treatment usually not curative

In infants the presenting symptom is vomiting (Cahill *et al.*, 1969), usually from birth (Burke, 1959). The vomit was bloodstained in 89% of Burke's series. The vomiting may be projectile, thus giving rise to the suspicion of pyloric stenosis; indeed the conditions may coincide (Burke, 1959; Smellie, 1954). Reflux oesophagitis leads to anaemia. This is a common presenting symptom and its degree is related to the severity of the oesophagitis. The babies are underweight; 45% of Burke's series were under the third percentile for weight, while 70% of Cahill *et al.*'s series were under the tenth percentile. Only four out of 85 babies in Burke's series had reached the 50th percentile for weight at their first attendance. The diagnosis of disease due to reflux oesophagitis in a baby is therefore unlikely if the weight is normal.

Dysphagia or vomiting during or immediately after feeds is suspicious of an oesophageal stricture; this may be due to oesophagitis and spasm and therefore be reversible, or to a fibrous stricture. Only treatment will determine which is present. However, fibrous stricture is rare below the age of two (Carré, 1975).

The babies may present with failure to thrive, to the extent of cachexia due to rumination (Herbst *et al.*, 1971).

The patient may present to the neurologist with abnormal athetoid movements associated with hiatus hernia and reflux, and relieved by curing the hernia (Sandifer's syndrome, Sutcliffe, 1969).

Hiatus hernia and reflux oesophagitis may be a familial condition (Burke, 1959). The association with pyloric stenosis has already been mentioned. Mental retardation is associated with the hiatus hernia reflux syndrome (Lari and Lister, 1971; Burke, 1959; Jewett and Waterston, 1975).

Pulmonary infections are commoner in babies who reflux, *i.e.*, vomit at night and inhale (Carré, 1960).

In adults there is an increased incidence of gall bladder disease of 27% (Allison, 1973) and of peptic ulcer.

Diagnosis of oesophageal reflux and hiatus hernia

Radiology is just one of several ways of making this diagnosis. Intraluminal pH and pressure measurements will give the same clinical information and even radioisotopes can now be used. However, radiology is, at the moment, the simplest and least unpleasant way of making the diagnosis. It is evident from the discussion above that an hiatus hernia is quite consistent with good health, and that gastro-oesophageal reflux and its effects are the main condition we have to assess. Nevertheless an attempt to diagnose an hiatus hernia should be made for the following reasons:

(1) Stomach content passing above the diaphragm is harmless if it remains in the stomach, but can cause inflammation in the oesophagus. The oesophageal junction should therefore be identified.

(2) To diagnose a cause of stricture in the gullet and differentiate it from a carcinoma of the oesophagus.

(3) To give the surgeon the anatomy of the region.

The radiological procedure is the same for adults and infants. The patient is given barium to drink lying supine and prone oblique turned to his left. The oesophagus and oesophago-gastric junction are observed on the TV monitor. The site of the inferior oesophageal sphincter (the first constant area of hold up or narrowing in the gullet) is noted. This may only become evident with different degrees of filling of the gullet (Figs. 4 and 5). The video recorder is very helpful in difficult cases. A note is made whether there is hold up of the barium at the hiatus. This occurs on inspiration and is relieved by expiration. It is a normal finding and not related to the position of the inferior oesophageal sphincter.

When the stomach is full the patient is turned from side to side, varying abdominal compression applied (in the case of an infant, by hand, while an adult lies prone over a bolster), and the patient tilted about 15% head down. The presence of reflux, its extent and ease of production, the presence of an hiatus hernia and of an oesophageal stricture are noted. Finally, the stomach and duodenum are examined for evidence of peptic ulceration and pyloric spasm or stenosis.

SIGNIFICANCE OF REFLUX

This is a difficult question to answer, since there is poor correlation between the clinical symptoms of acid regurgitation and heartburn with the radiological demonstration of reflux.

Asymptomatic patients may have reflux on radiology (Venkatachalam *et al.*, 1972); symptomatic patients may have none. A similar discrepancy exists between the finding of reflux and of oesophagitis on endoscopy.

The difficulty is further increased in infants who cannot complain and in whom intermittent reflux is normal, particularly if they are crying and intermittently swallowing at the same time and, of course, if somebody is pressing on their abdomen. So reflux is most significant if it is demonstrated when the infant is quiet, if it is extensive, and if it occurs in the correct clinical context of a baby that is vomiting, anaemic and failing to thrive.

The presence of an oesophageal stricture immediately makes reflux significant. In infants reflux oesophagitis can be diagnosed by a shaggy appearance of the oesophageal wall (Fig. 9).

DIAGNOSIS OF HIATUS HERNIA

This is made by finding some of the following:

(a) A supradiaphragmatic inferior oesophageal sphincter (Figs. 6 and 9);
(b) Gastric mucosal folds above the hiatus (Figs. 6 and 7);
(c) A very wide hiatus or a very wide portion of the gullet above it (Fig. 7);
(d) Finding a lower oesophageal ring or notch above the diaphragm.

These rings and notches are mostly evanescent structures often only seen on full distension of the oesophagus. Although their radiographic appearance, aetiology and significance have been clearly described (Schatzki and Gary, 1953, 1956; Schatzki, 1963, 1965; Friedland *et al.*, 1966; Goyal *et al.*, 1970) it sometimes happens that the individual radiologist remains uncertain of the significance of his findings. Fortunately, this uncertainty usually arises in patients without symptoms referable to the oesophagus where the findings are of no direct clinical significance. There is, therefore, hardly ever operative or pathological confirmation of the findings. The following illustrations show the types of lower oesophageal rings and notches.

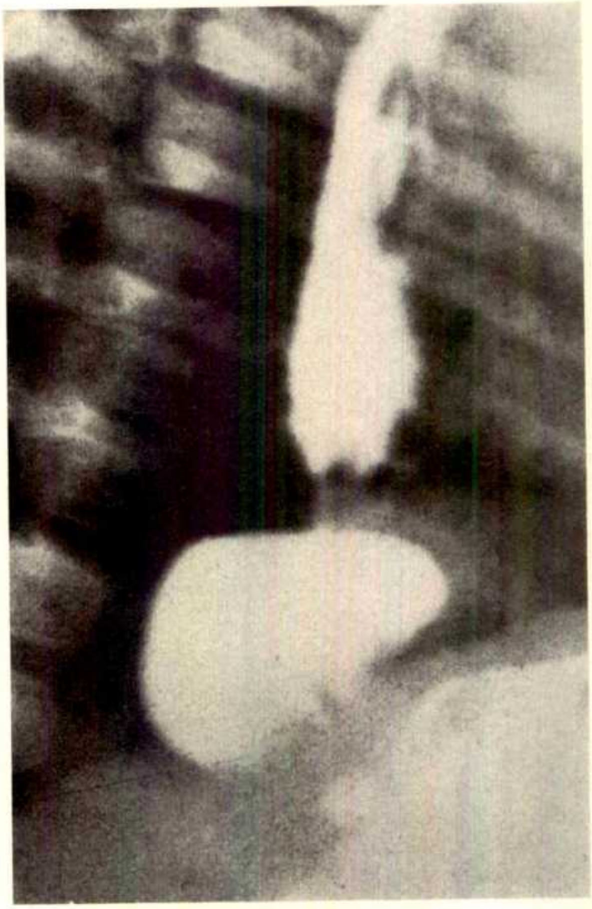


FIG. 9.

Hiatus hernia—inferior oesophageal sphincter above diaphragm. Narrowing at hiatus. Irregular oesophageal wall due to reflux oesophagitis. (Patient later developed a stricture.)

Figure 6A: This notch at the apex of the hernia in the barium filled stomach is often seen and corresponds to the incisura (and the sling fibres of the stomach). This is clearly seen on the mucosal film taken erect (Fig. 6B).

Figure 10: This kind of notch on the left side of the gullet, according to Friedland *et al.* (1966), represents either the sling fibres of the stomach or the left edge of transverse mucosal fold and constrictor cardiae muscle, and therefore marks the level of the incisura. By these criteria, therefore, this

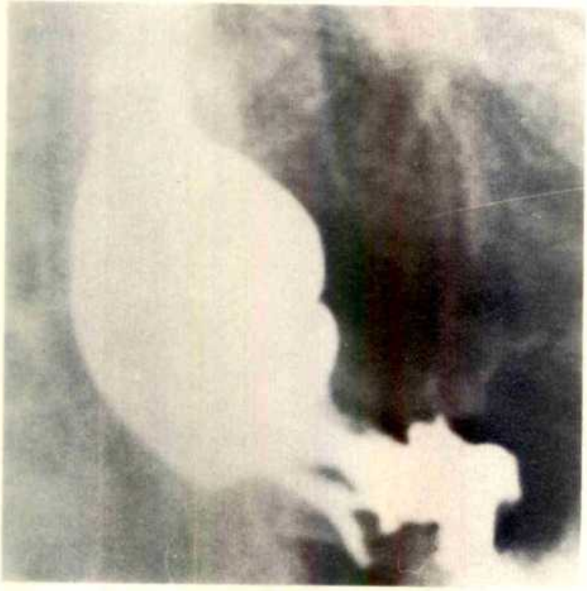


FIG. 10.
Notch in left side of gullet. ? cause. Patient did not have gastro-oesophageal reflux or other evidence of hiatus hernia. Film taken while swallowing.

patient had an hiatus hernia, although he did not have any other radiological evidence of this.

Figure 3: This is the author's understanding of a Schatzki ring. Schatzki described a ring about 4–5 cm above the diaphragm 2–4 mm thick in patients suffering from intermittent dysphagia. He (Schatzki, 1965) and MacMahon *et al.* (1968) considers that this ring marks the site of the junction of oesophageal mucosa with gastric, and could therefore be used to assess the site of the oesophageal junction. This finding was confirmed by Goyal *et al.* (1970) in 10% of their material. The patient illustrated had no symptoms referable to the oesophagus or the oesophago-gastric junction. These rings are very rare in adults (the author has not seen a similar ring in the last 1000 barium examinations, although all his patients swallowed barium in the prone position). They have not been reported in children.

Figure 11: Occasionally the "Schatzki" ring is in fact a diaphragm across the gullet as in this child.

Figure 12: This constant thick ring in the distal gullet is at the site of the inferior oesophageal sphincter and most probably represents a muscular ring. These rings can lead to dysphagia.

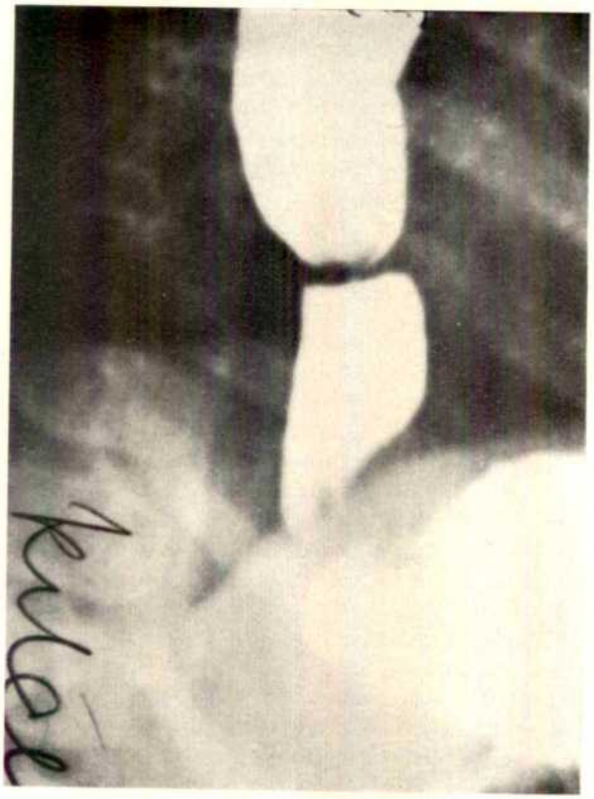


FIG. 11.
Dysphagia in infant caused by mucosal diaphragm.

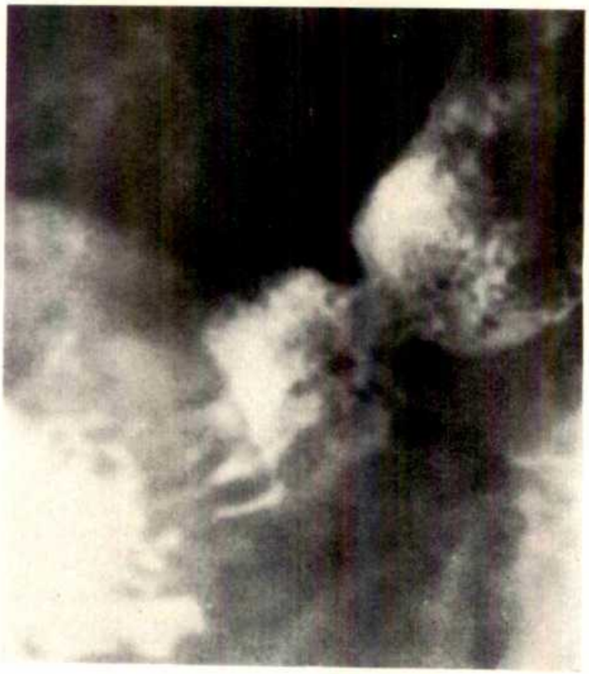


FIG. 12.
Muscular ring in distal oesophagus.

Prognosis

This depends on the age. Over 90% of infants presenting with reflux oesophagitis recover on upright nursing and thickening of feeds. Some recover very quickly, while some take up to early childhood to make a full clinical recovery. Patients with persistent failure to thrive, anaemia, oesophagitis or stricture need operation. In adults medical treatment is less likely to succeed (Behar *et al.*, 1975).

Conclusion

Radiology remains the most convenient and readily available method of assessing the oesophagogastric junction. The radiologist must be aware that reflux oesophagitis can be a very debilitating condition—particularly in infants in whom it can lead to severe failure to thrive, even to marasmus. Oesophageal strictures may form. The condition should therefore be suspected in any infant presenting with the return of food and failure to thrive. Adults will usually give a history of heartburn and epigastric pain. However, any case of oesophageal stricture should always be examined for reflux and hiatus hernia, and a carcinoma excluded. Care should be taken over the barium examination. All patients should be examined in the horizontal position (both during swallowing the barium and later head down with a full stomach).

Fortunately for the radiologist the all-important diagnosis of gastro-oesophageal reflux and its complications is easy (but beware the intermittent refluxer!), while the less important diagnosis of hiatus hernia can present considerable difficulty at times. However, even when the diagnosis of reflux has been made its significance must be assessed in relation to the patient's clinical condition. Further investigations, such as endoscopy, may then be needed for further assessment.

Acknowledgments

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Book reviews

Handbuch der Medizinischen Radiologie—Encyclopedia of Medical Radiology Vol. V, Part 1.
Röntgendiagnostik der Skeletterkrankungen—Diseases of the Skeletal System (Roentgen Diagnosis). Ed: L. Diethelm, pp. x+849 (Springer-Verlag, Berlin, Heidelberg, New York). $262.40.

This is the first of the six volumes dealing with the pathological radiology of the skeletal system. It is divided into two parts. The first part describes the formation, growth, and structure of normal bone and the deviation from normal. Illustrations are good and consist of radiographs and numerous pictures of macerated sections of bone. There are comprehensive sections on densitometry and morphometry. There are short sections on heterotopic bone formation and the radiology of joint diseases.

Part two deals comprehensively with the effects of heat, cold, electricity, radiation and alterations of blood supply, on bone. There is a chapter in English on myelosclerosis. The references are comprehensive and extend up to 1975.

This is a highly academic book dealing in its first part with general principles of bone formation and in its second part with unusual conditions in which bone pathology is rarely thought to be of prime clinical importance. It is therefore more likely to appeal to the research student than to the practising radiologist looking for the answer to a clinical problem.

M. Steiner.

Handbuch der Medizinischen Radiologie—Encyclopedia of Medical Radiology, vol. VI, part 3.
Röntgendiagnostik der Wirbelsaule—Roentgen Diagnosis of the Vertebral Column. Ed: L. Diethelm, pp. xx+880 (Springer-Verlag, Berlin, Heidelberg, New York), $239.90.

We are told in the preface that this book took 15 years to write—it must indeed be the most complete text on normal and abnormal spinal curvature available. There are clinical, radiological and pathological descriptions of all conceivable conditions leading to kyphosis, lordosis and scoliosis. The effects of these abnormal curvatures on the lungs, heart, abdominal organs and pregnancy are described. Treatment of the curvatures together with its complications are discussed. There are 120 pages of references up to 1974. The illustrations are good and the index and lists of contents well arranged and easy to use. The book contains everything a radiologist is likely to wish to know about spinal curvature, whether to make a diagnosis or to discuss the case.

Both books suffer from the major drawback of their price. Only the individual can decide whether each of these books is worth four or five expensive "ordinary" books in English.

M. Steiner.

1977, *British Journal of Radiology*, *50*, 175–180 MARCH 1977

Percutaneous transhepatic cholangiography using the "Chiba"* needle—80 cases

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ABSTRACT

Using the Chiba needle for percutaneous transhepatic cholangiography, bile ducts have been visualized radiographically in 80% of 80 patients with cholestatic jaundice. The success rate was 94.4% in the 54 patients with dilated bile ducts due to an extrahepatic bilary obstruction, and 50% of the 20 patients with undilated ducts. Four patients developed ascending cholangitis with septicaemia on the same day as the procedure, and early surgery after visualization of obstructed bile ducts is recommended. The technique was successful in three of five patients with sclerosing cholangitis. Percutaneous cholangiography using the Chiba needle is a convenient method of opacifying the biliary system in patients with severe large bile duct obstruction.

Improved techniques for the radiographic visualization of the biliary system allow better investigation of cholestatic jaundice, and operative surgery is no longer necessary for primary diagnosis. Endoscopic retrograde cholangiography (ERC) has a success rate of 74–94% in specialist centres (Cotton, 1972; Blumgart *et al.*, 1972). It can, however, be a difficult and time-consuming technique, the endoscopes are costly, and only the lower margin of a tight lesion obstructing the biliary tract is shown. High dose intravenous infusion cholangiography may opacify the large bile ducts in moderately severe jaundice, but may fail to supply sufficient anatomical detail because of dilution of the contrast medium with bile (Scholz *et al.*, 1975). Percutaneous transhepatic cholangiography (PTC) using the Chiba needle (Okuda *et al.*, 1974) offers several advantages over the older anteriorly introduced sheathed needle where an aspirating technique is used. The lateral insertion enables the operator to inject contrast medium continuously while withdrawing the needle under fluoroscopic control, without exposing himself to excessive radiation. The flexibility of the needle enables the patient to breathe normally throughout the procedure without trauma to the liver or its capsule. Initial reports show that normal bile ducts are frequently cannulated, and even in the presence of complete biliary obstruction, immediate surgery may not be necessary (Okuda *et al.*, 1974; Redeker *et al.*, 1975).

A randomized trial to compare ERC with PTC for bile duct visualization showed an overall success rate using the Chiba needle of 56.8% in 44 examinations. The success rate was 95% in extrahepatic cholestasis and only 25% for patients who were found to have intrahepatic cholestasis (Elias *et al.*, 1976). Following this trial, PTC has been performed on 80 additional patients with cholestatic jaundice. The indication for the procedure was to confirm or exclude large bile duct obstruction and in each case oral or intravenous cholangiography was impossible because of deep jaundice, or had previously given unsatisfactory results.

PATIENTS AND METHODS

All 80 patients had cholestatic jaundice. Eleven were known to have primary biliary cirrhosis, but deepening jaundice or right upper quadrant pain made the presence of common bile duct stones possible, as cholelithiasis is common in primary biliary cirrhosis (Summerfield *et al.*, 1976). The other 69 patients were considered to have probable large duct obstruction requiring investigation (Table I).

The Chiba needle was used as previously described (Okuda *et al.*, 1974; Elias *et al.*, 1976). Antibiotic therapy was started between 1 and 24 hours before the procedure, which was performed only if the prothrombin time was no more than three seconds prolonged over control. Intravenous diazepam was used as premedication, and local anaesthesia was achieved with lignocaine 1%, in the 7th, 8th or 9th intercostal space in the mid-axilary line. The intercostal space was chosen by maximal dullness to percussion and the position of the liver by preliminary X-ray of the abdomen when the patient was prepared in the supine position. The highly flexible Chiba needle was then introduced into the liver parallel to the table top, and perpendicular to the spine, until judged to have reached the depth of the right border of the spine. After removal of the stylette, contrast medium (Hypaque 45 or Conray 280) was injected continuously while withdrawing the needle under fluoroscopic vision. Structures

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*Chiba needles manufactured by Messrs. V. J. Millard, 36 Highgate Hill, London, N19.

TABLE I

Patients studied

	Number	Success	Fail
Total	80	64	16
Stone in CBD	20	16	4*
Post-surgical stricture	12	12	0
Ca pancreas	11	9	2
PBC—no obstruction	10	5	5
Ca bile duct	6	6	0
Sclerosing cholangitis	5	3	2
Secondary carcinoma	4	4	0
Cholestatic hepatitis	3	2	1
Chronic pancreatitis	2	2	0
Ca ampulla of Vater	2	2	0
Ca gall-bladder	2	2	0
PBC with stone in CBD	1	1	0
Empyema of gall-bladder	1	0	1
Biliary atresia	1	0	1

*Procedure abandoned in one patient after two insertions of the needle

PBC—Primary Biliary Cirrhosis.

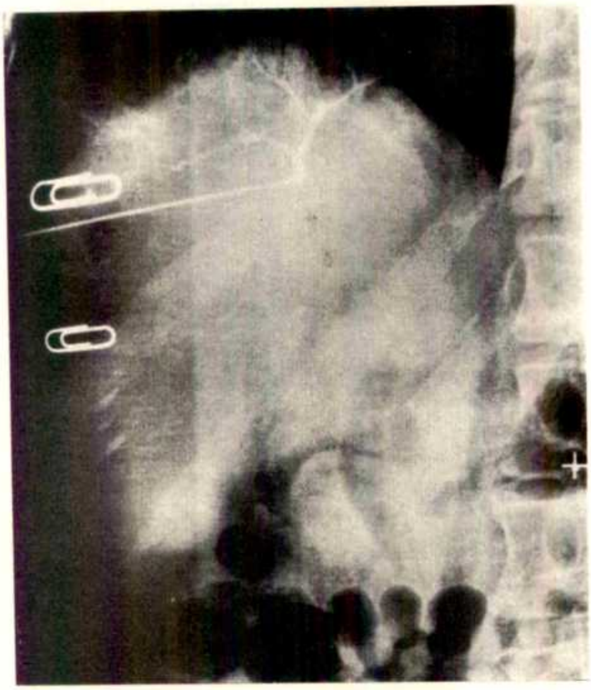

Fig. 2

A peripheral branch of a portal vein outlined by continuous injection of contrast medium.

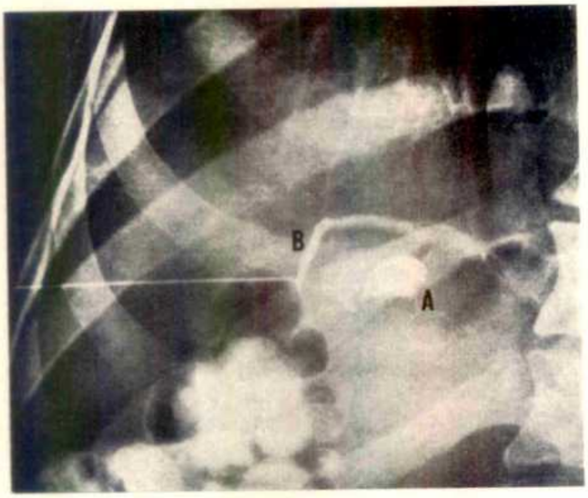

Fig. 1.

Parenchymatous deposit (A) and hepatic vein (B). There is barium in the ascending colon.

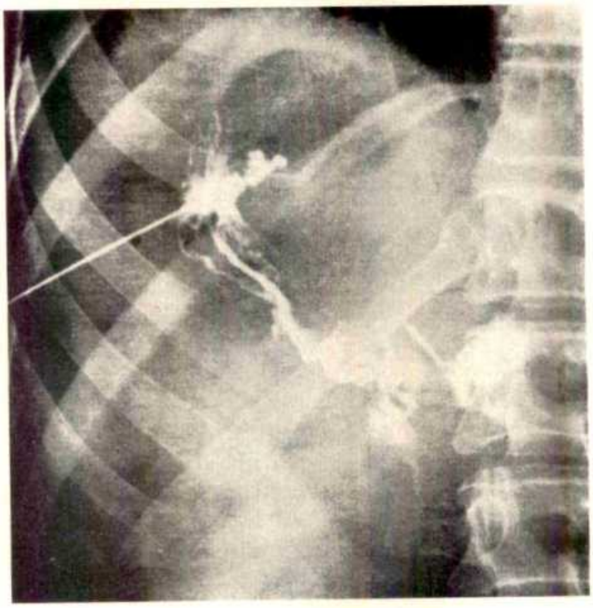

Fig. 3.

Lymphatics from parenchymatous deposit to gastrohepatic ligament and coeliac lymph node.

other than bile ducts were frequently opacified. Injection into liver parenchyma resulted in a localized deposit of contrast which was slow to clear (Fig. 1). Portal and hepatic veins were recognizable by the direction of flow, and rapid disappearance of contrast medium when injection was stopped (Figs. 1 and 2). Entry of the needle into a hepatic vein radicle frequently led to persistent filling of that vein through the tract made when the needle was withdrawn and more contrast injected. Lymphatics could be filled, usually after injection of contrast into hepatic parenchyma (Fig. 3). These were recognized by their characteristic size, multiplicity and direction of flow, coursing with the portal tracts to the hilum of the liver, then in the gastrohepatic ligament to the coeliac lymph nodes overlying the region of 12th thoracic vertebra (Goldberg *et al.*, 1975). Radiopaque contrast took five to ten minutes to be cleared from the lymphatic channels. When contrast medium entered a bile duct it flowed in both directions, cleared slowly, and further injection usually filled several adjacent radicles, particularly if outflow into the duodenum was obstructed. If bile ducts were not entered during the first withdrawal of the needle, it was re-inserted up to five times with some change in its direction each time, before the examination was abandoned. The procedure caused minimum discomfort to the patient unless contrast medium was inadvertently injected under the capsule of the liver.

After injection of contrast medium into obstructed and dilated bile ducts, the picture of high duct obstruction was frequently seen (Fig. 5). In this circumstance, it is essential to tilt the patient upright and take a further film after 30 minutes, as this may be the early picture of low duct obstruction, with slow filling of the common bile duct with diluted

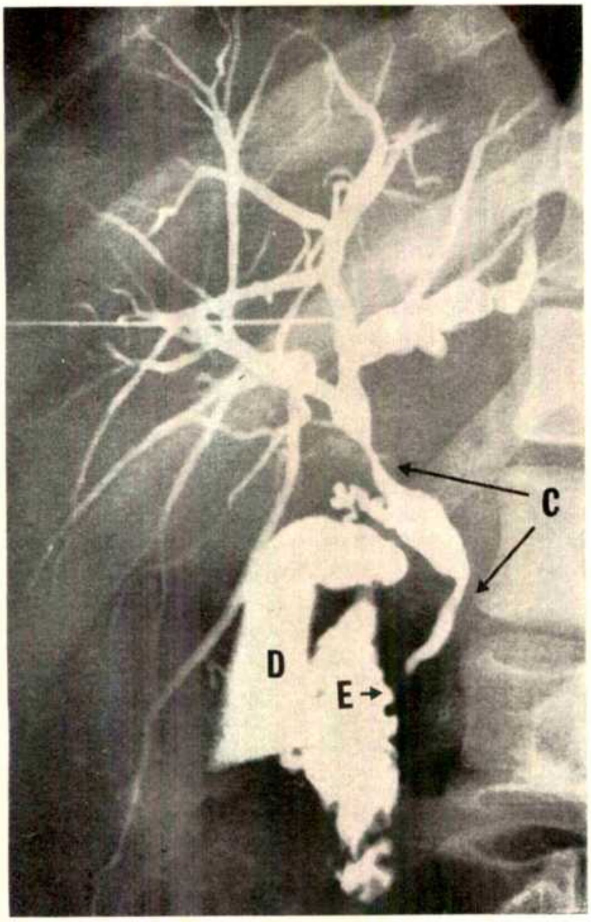

FIG. 4.

Sclerosing cholangitis with narrowed segments of bile ducts (C). Gall bladder is filled (D) and contrast medium flows into duodenum unobstructed(E).

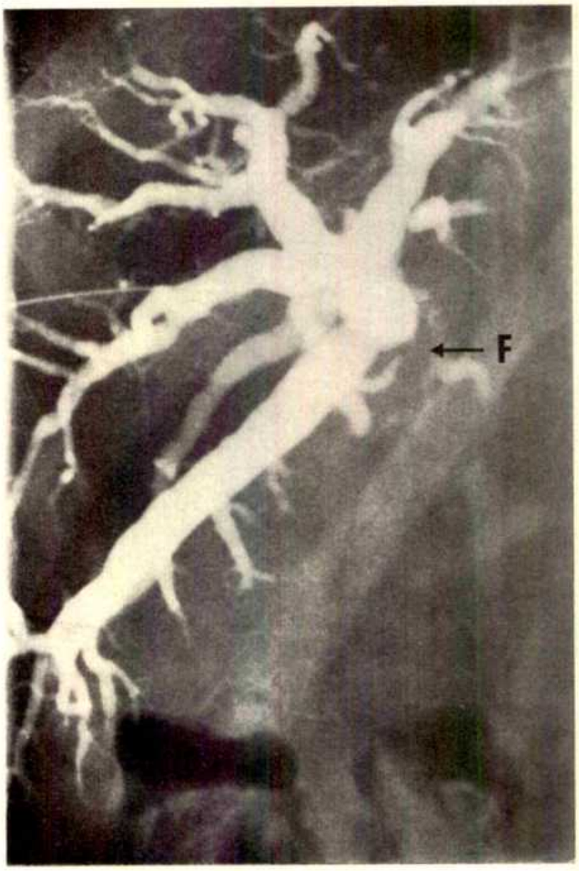

FIG. 5.

Early picture shows dilated intra-hepatic bile ducts with suspected block at the hilum (F).

TABLE II

NUMBER OF INSERTIONS BEFORE SUCCESS IN PATIENTS WITH DILATED AND UN-DILATED BILE DUCTS

	Number of insertions							
	1	2	3	4	5	6	Not recorded	Unsuccessful
Dilated ducts—53 patients	21	14	4	2	3	3	3	3
Undilated ducts—27 patients	3	2	3	2	0	2	2	13

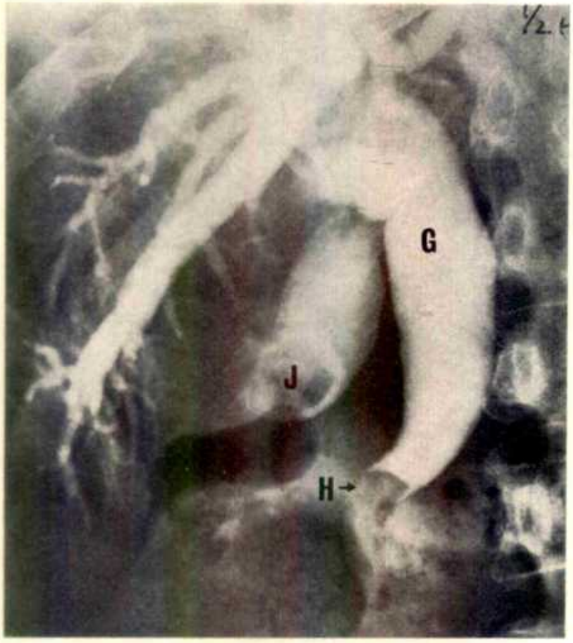

FIG. 6.

Same patient as Fig.5, 30 minutes later common bile duct is opacified and dilated (G). A stone is blocking the ampulla of Vater (H) and there is a stone in the gall-bladder (J).

contrast medium. Figure 6 shows the same patient after this procedure was employed, the later film showing a stone wedged in the ampulla of Vater.

RESULTS

Bile duct visualization was achieved in 64 of the 80 patients (Table I), an overall success rate of 80%. The investigation was considered to be satisfactory when it showed either unobstructed bile ducts, or the anatomical site of an obstruction which was later confirmed by surgery. In one of the 64 cases where bile ducts were entered, PTC showed the picture of a high obstruction with no contrast medium entering the common bile duct despite tilting the patient and waiting for 30 minutes, and a malignant lesion was suspected. Subsequent surgery however showed the obstruction to be due to stones low in the common bile duct.

In the 16 unsuccessful attempts at PTC, the final diagnosis (Table I) was subsequently established by ERC (10 cases), surgery (4 cases) or liver biopsy (2 cases). In one of these patients the examination was abandoned after two insertions of the needle because of severe pain and hypotension which were adverse reactions to the injected medium.

Bile ducts were more frequently visualized if they were dilated. When the appearance of the bile ducts was considered, either by PTC in the successful cases, or ERC or surgery with operative cholangiography in the remainder, dilatation of at least some part of the large bile duct system was apparent in 54 of the 80 patients. The 26 patients with undilated ducts were made up of 15 with intrahepatic cholestasis and 11 with extrahepatic cholestasis. The success rate of PTC was 51 out of 54 (94.4%) for patients with dilated ducts, and 13 out of 26 (50%) for patients with no dilated bile ducts.

The number of insertions of the needle needed to achieve bile duct visualization was recorded in 59 of the 64 successful examinations. In the presence of dilated ducts, success was usual after the first or second insertion (Table II). If there was no dilation of the bile ducts the distribution of successful attempts was more even. Success at the sixth pass of the needle suggests that even more attempts would improve the rate of bile duct visualization whether or not they are dilated.

COMPLICATIONS

Four patients developed cholangitis within half to six hours after PTC despite prophylactic antibiotic therapy. Two had stones in the common bile duct, one sclerosing cholangitis with a common bile duct structure, and one had a surgical stricture. All four patients has a history of previous cholangitis, but a similar history was obtained in 22 of the 64 patients where ducts were visualized. The incidence of cholangitis was therefore 4 out of 64 (6.25%) for successful procedures, and 4 out of 22 (18.2%) for

TABLE III

COMPARISON OF SUCCESS RATES AND COMPLICATIONS IN FOUR CHIBA NEEDLE SERIES AND ONE USING SHEATHED NEEDLE

	Total number	Overall success rate, %	Surgical/ Extrahepatic, total number	Success rate, %	Medical/ Intrahepatic, total number	Success rate, %	Complications, %
George *et al.*	137 (sheathed)	70.8	112	83.9	25	12	Not recorded
Okuda *et al.*	314 (Chiba)	85.3	234	91.5	80	67.5	7.6
Redeker *et al.*	40 (Chiba)	80	20	100	20	60	5
Elias *et al.*	44 (Chiba)	56.8	20	95	24	25	6.8
Jain *et al.*	80 (Chiba)	80	60	90	15	46.7	6.25

those with previous cholangitis which was frequently associated with common bile duct stones and surgical strictures. When the procedure abandoned because of adverse reactions to the contrast medium was included, the total incidence of significant complications was 5 out of 80, also 6.25%.

DISCUSSION

Comparison of our results with previous series using the Chiba needle or the sheathed needle is complicated by differences in the classification of the patients studied. Okuda *et al.* (1974) divided their patients into those with surgical and non-surgical hepatobiliary disease, and Redeker *et al.* (1975) into those with proved biliary tract obstruction, and those with undilated, unobstructed bile ducts. Elias *et al.* (1976) called the groups extra- and intrahepatic cholestasis. To divide the patients in this series into the two comparable groups, surgical or extrahepatic cholestasis, and non-surgical or intrahepatic cholestasis, the five patients with sclerosing cholangitis must be excluded as they do not readily fall into either group. Bile ducts were successfully visualized in three of these patients (Fig. 4). The cholestatic jaundice of chronic pancreatitis (Warshaw *et al.*, 1976; Scott *et al.*, 1976) is included in the surgical extrahepatic group. Comparison now shows that the improved rate of duct visualization achieved in this current study (80%) compared with that previously reported from this unit is due to better results in the non-surgical intrahepatic cholestasis group. The success rate was 54 out of 60 (90%) in surgical extrahepatic jaundice and 7 out of 15 (46.7%) in non-surgical intrahepatic cholestasis (Table III). This is still a lower success rate than the Okuda and Redeker series, but may reflect practice and improvement in our technique. The other major difference is that we do not have a 100% success rate for patients with biliary tract obstruction, and this diagnosis cannot be excluded with certainty by failing to opacify bile ducts.

The incidence of significant complications is similar to previous series (Table III), and occurred only in patients with lesions obstructing the extrahepatic biliary system. Contrary to previous recommendations (Okuda *et al.*, 1974; Redeker *et al.*, 1975) this series confirms that on finding an obstructing lesion on PTC, our practice of proceeding to operative surgery on the same day as the investigation is correct (Elias *et al.*, 1976), and the delay of up to six hours, during which time four of our patients developed cholangitis, would appear to be too long.

The incidence of cholangitis after the procedure would certainly be reduced if, after entry into dilated bile ducts is confirmed by injection of a small amount of contrast medium under fluoroscopy, the biliary system could be decompressed by aspiration of bile. This has not been possible in our hands probably because of the internal diameter of the needle used is slightly smaller than that of Okuda *et al.* (0.5 mm), and the bile is too viscous to be aspirated through the needle. This is possible with the sheathed needle where infected bile may be drained preoperatively in a severely ill patient with cholangitis, biliary tract obstruction and septicaemia, and is an advantage of that technique. Controlled comparison of the two procedures has not been made, but in one review the success rate in 1629 procedures using the sheathed needle was 74% (Hines *et al.*, 1972), which is comparable to the results in this series. When patients with intrahepatic cholestasis were analysed separately the success rate with the sheathed needle was only 12% (George *et al.*, 1965).

The principal advantages of the Chiba needle technique are that it is a simple and relatively atraumatic procedure which is usually very well tolerated by the patient, and which need be followed by operative surgery only if biliary obstruction is found. The overall success rate for the procedure is slightly higher than that of the sheathed needle technique, and much higher for patients with intrahepatic cholestasis.

Addendum

Since this paper was submitted we have used a 22 gauge needle (external diameter 0.71 mm, internal diameter 0.42 mm) instead of the 23 gauge needle (external diameter 0.64 mm, internal diameter 0.33 mm) used in this paper. With this larger needle we can aspirate bile and have had no septicaemic complications. It is possible that aspiration of bile may reduce the incidence of cholangitis and septicaemia seen in the above series.

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Bone thinning in frontal mucocele

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(*Received August, 1976*)

ABSTRACT

Sixteen cases of frontal mucocele are reviewed. Bone thinning leading to destruction of the sinus floor was shown to be a feature. It usually affects the superomedial margin of the orbital roof first, due to pressure on the area where the sinus wall is thinnest. Demonstrable thinning of either anterior or posterior sinus walls—a cardinal sign of frontal mucocele, is best shown by means of underpenetrated lateral radiographs.

All other conventional radiographic signs of frontal mucocele, including lucency of the affected sinus, were found to be non-specific. The presence of an osteoma in a site likely to obstruct the frontonasal duct is a valuable adjunct to diagnosis.

The radiographic lucency paradoxically shown in some frontal mucoceles is the result of a thinning of the walls of the sinus, which can be demonstrated by means of soft tissue lateral radiographs. Schwörer *et al.* (1972) proved in experiments with models that the image cast by a fluid-filled cavity will be less dense if its walls are thin.

An attempt is made in this paper to define the radiological profile of mucoceles of the frontal sinus and to outline differential diagnostic criteria in respect of other lesions.

CASE MATERIAL AND FINDINGS

Sixteen cases of frontal mucocele from the Wessex Neurological Centre, Southampton and the Liverpool Ear, Nose and Throat Infirmary were studied. The commonest clinical presentation (13 out of 16 patients) was a painless and non-pulsating unilateral proptosis. In three patients the proptosis was severe enough to have produced double vision. Sinus pain was a prominent feature in only one patient (Case 15, Table I), and only two others complained of pain in the region of the eyes and forehead. In Case 6, a patient undergoing treatment for nasal polyp, the frontal mucocele was a chance finding.

Standard radiographic views of the paranasal sinuses were available, including occipito-frontal, occipito-mental, and lateral projections. Several patients were also examined by tomography of the frontal sinuses.

The radiological features are given in Table I. In the coronal views, the main finding was destruction of the supero-medial margin of the roof of the underlying orbit. Increased sinus opacity was present in nine patients, this appearance being consistent with a fluid-filled sinus. No fluid levels were seen. Of the remaining seven patients, three had hyperlucent frontal sinuses. Osteomata were seen in three patients, situated in sites considered likely to obstruct the frontonasal duct. Sclerosis of the bony margin of the affected sinus was present in five of the 16 patients. In lateral projections bone thinning was convincingly demonstrated in a total of nine patients; underpenetrated films showed it better.

TABLE I

RADIOLOGICAL FEATURES OF 16 PATIENTS

Cases	Orbital erosion	Bone thinning	Osteoma	Increased sinus density	Sclerotic margin
1 Female, 58, Painless proptosis, diplopia	+	+	—	+	+
2 Female, 53, Painless proptosis, diplopia	+	—	—	+	—
3 Male, 79, Painless proptosis	+	+	—	—	+
4 Male, 73, Painless proptosis	+	+	—	+	—
5 Female, 60, Painless proptosis, diplopia	+	—	—	+	+
6 Female, 36, Nasal polyp	+	—	—	—	—
7 Female, 76, Painless proptosis	+	+	—	—	—
8 Male, 75, Painless proptosis	+	—	—	+	—
9 Female, 64, Painless proptosis	+	—	—	—	—
10 Female, 56, Painless proptosis	+	+	+	+	—
11 Male, 50, Pansinusitis	—	+	—	+	+
12 Male, 56, Pain round eye, proptosis	—	+	—	—	—
13 Male, 54, Painless proptosis	+	—	+	+	—
14 Female, 46, Painless proptosis	—	—	—	+	+
15 Male, 48, Pansinusitis	+	+	—	—	—
16 Male, 46, Painless proptosis	+	+	+	—	—

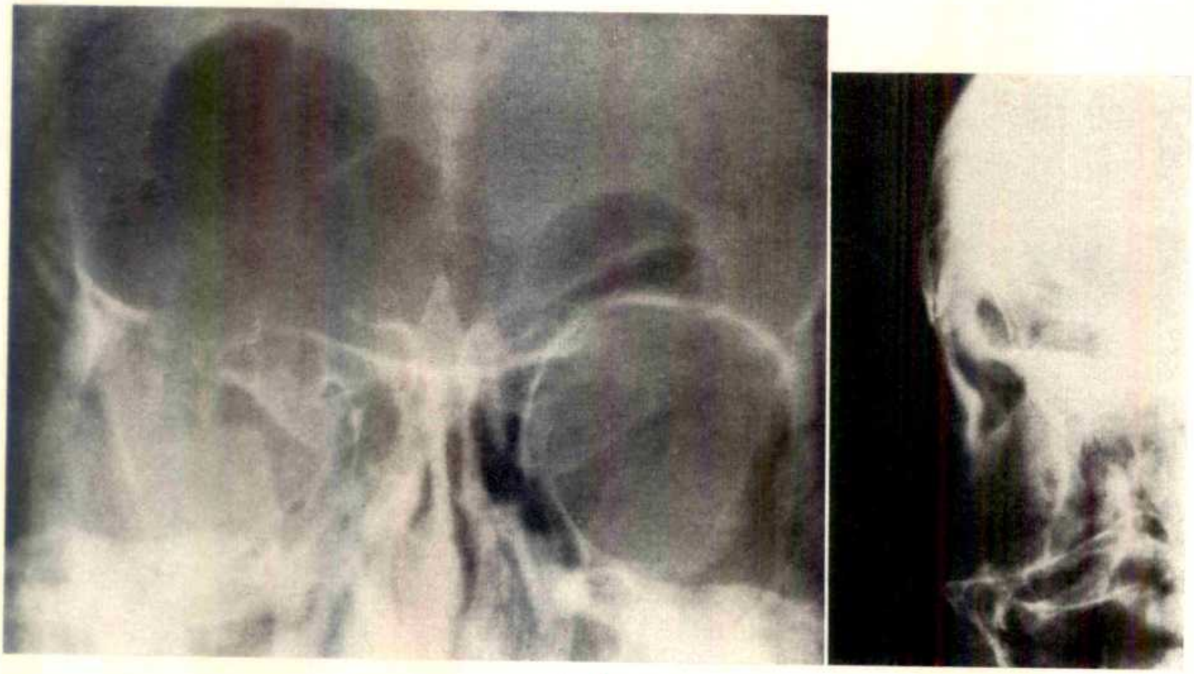
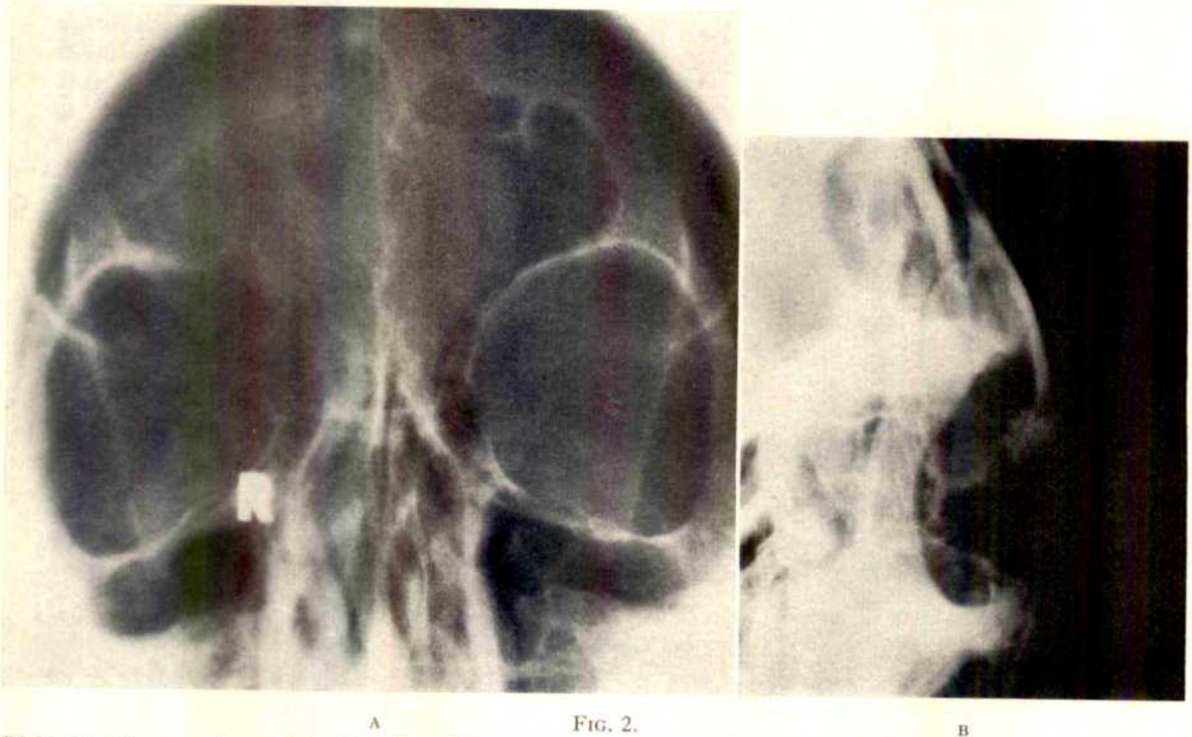

A B

FIG. 1.

Right frontal mucocele—occipito-frontal and lateral projections. There is loss of the superior orbital margin, the sinus is lucent. The lateral projection shows a sinus of small depth with a thinned anterior wall.



A B

FIG. 2.

Right frontal mucocele—occipito-frontal and lateral projections. Loss of the superior orbital margin, but a sinus of increased density. The lateral projection shows a sinus of increased depth.

TABLE II

DEPTH OF FRONTAL SINUS (CM)

Bone thinning with increased opacity	Bone thinning with lucent sinus	Control group	
2.4	1.2	1.1	2.0
2.7	1.4	2.3	0.9
2.2	1.6	0.7	0.9
1.9	1.1	0.8	1.1
	0.8	0.7	1.8
		1.5	1.0
		0.8	0.9
		1.7	0.7
		0.5	2.6
		0.9	1.4

The depth of the frontal sinus was measured in three groups (Table II): (1) cases of frontal mucocele exhibiting bone thinning and increased opacity of the sinus—four patients; (2) cases with frontal mucoceles exhibiting bone thinning and lucent or hyper-lucent sinuses—five patients; and (3) a randomly-selected control group—20 subjects. The findings (Table II) showed that a significantly greater average sinus depth was present in the Group 1 patients than in the other groups.

DISCUSSION

Frontal mucocele accounts for 15% of the patients with unilateral exophthalmos presenting to an ear, nose and throat surgeon (Zizmor and Noyek, 1968) and 3% of those presenting to an ophthalmic surgeon (Reese, 1963). Most authors (Wolfowitz and Solomon, 1972; Iliff, 1973) agree that pain is not a feature of the condition. However, Bordley and Bosley (1973) found a high incidence of headache in a series of cases which was notable for its high complication rate.

The characteristic radiological finding in this series was destruction of the layer of bone separating the sinus from the orbit, which is the thinnest part of the sinus wall (Cunningham, 1972). Consequently this is its weakest part and it will be affected first by an expanding lesion of the frontal sinus.

Thinning of the anterior and posterior sinus walls may be demonstrated in lateral projections—it was present in nine of the 16 patients reviewed. If convincingly present, it represents a reliable sign of mucocele.

The patients in whom a combination of bone thinning and increased opacity was present, possessed a greater average antero-posterior diameter of the frontal sinuses than was shown either in those patients in whom one or other of these features was present alone, or in the controls. The antero-posterior diameter of the control group varied widely, from 0.5 to 2.6 cm, averaging 1.2 cm. According to Gray (1973) the average diameter of the frontal sinus is 1.8 cm. These measurements are significantly lower than the average of the group showing a combination of bone thinning and increased opacity, namely 2.3 cm. The wide variation in the control group confirms that it is impossible to diagnose pathological antero-posterior expansion of a sinus in any individual patient without the benefit of serial radiographic examinations.

Loss of the normal sclerotic sinus margin is said to be an early change in mucocele, which occurs prior to expansion of the sinus (Samuel, 1968), and the findings in nine patients confirm this. Loss of the convoluted pattern of the affected sinus (Wolfowitz and Solomon, 1972) and deviation of the intersinus septum towards the unaffected side are also believed to be unreliable signs, unless confirmed by serial examinations. In life the frontal sinuses are usually asymmetrical, and deviation of the intersinus septum is a common normal variant (Gray, 1973).

Squamous carcinoma of the frontal sinus, a rare entity, may present the same pattern of destruction in coronal views as frontal mucocele (Boone and Harle, 1968), but the lateral projection is said usually to show early destruction of the walls, rather than the typical thinning exhibited by a mucocele. Krüse and Neumann (1974), in a review of four cases of sinus disease in which the diagnosis was in doubt, claimed that surgical biopsy may be the only way of providing a definitive answer. Defects of cranial fusion such as meningocele and encephalocele of the frontal region in adults are said to mimic mucocele if the characteristic mid-line defect in the skull is not visible (Zizmor and Noyek, 1968). Plain-film changes, similar to a mucocele, were present in a 23-year-old patient with an olfactory neuroblastoma who presented at the Wessex Neurological Centre with a short history of pain and proptosis.

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Book review

Nuclear Medicine: Report of a joint I.A.E.A./W.H.O. expert committee on the use of ionizing radiation and radioisotopes for medical purposes (nuclear medicine). Technical Report Series 591, pp. 72, 1976 (World Health Organization, Geneva), Sw. Fr. 7.

The title of this report is somewhat misleading, as it could be construed to include X-ray diagnosis and beam radiotherapy, whereas it is concerned solely with administered radioisotopes. Nevertheless, it is a useful and surprisingly stimulating document. It follows an earlier report (1972) from the same organizations on the same subject, and a number of other related reports, mostly dealing with the training of various radiation staff. The members of the committee were drawn from many countries (mostly "developed") in four continents and clearly encompass a wide range of experience.

The first chapter deals with the development of nuclear medicine, its contribution to health and research and possible future trends.

The next three chapters make specific recommendations about the provision and organization of nuclear medicine facilities, suggested staffing and equipment. Together they would prove useful to any hospital, region or country embarking on a nuclear medicine service or enlarging existing facilities. Individual planners may find the schedules of floor area, suggested staff and equipment valuable for banging on the doors of funding authorities. There is a very sensible emphasis on the reliability of equipment and provision for maintenance, with specific suggestions for the duplication of items and in some circumstances investment in spare parts.

Thus far the report is competent, well-balanced, but predictable. Chapter 5 on the funding of nuclear medicine services paves the way for a most welcome and thought-provoking discussion of cost effectiveness in nuclear medicine. Techniques of evaluation of diagnostic procedures are described and examples given of their application in nuclear medicine. These ideas are further developed in four of the Annexes where useful lists of alternative non-nuclear procedures are included. No answers are given as to which procedures are most cost effective, but there is guidance on how the questions should be asked. These considerations are not unique to nuclear medicine, of course, and this section could be read with advantage by anyone concerned with diagnostic procedures who has not yet given attention to cost effectiveness. Investing in this report could be much more profitable than putting the money into a Swiss bank.

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Origin of the right vertebral artery from the right common carotid artery: angiographic demonstration of three cases

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ABSTRACT

Three cases are presented in which the right vertebral artery originates from the right common cartoid artery. The literature is reviewed and the significance of this anomally is discussed. It is suggested that this anomally occurs more commonly than indicated by previous reports.

In a recent communication, Bernardi and Dettori (1975), described two cases in which angiography demonstrated an aberrant right subclavian artery with the right vertebral artery originating as a branch of the right common cartoid artery. They considered this to be a rare anomaly and could find only one other record of angiographic demonstration of this anatomical variation.

The advent of transfemoral catheter techniques for examination of the intracranial circulation and cervical vessels has not only increased the potentiality of demonstrating such anomalies but has necessitated their recognition for correct technique and interpretation. All patients referred to this department for angiography of suspected extracranial arterial disease are examined by selective catheter studies of the right and left common carotid, innominate and left subclavian arteries (Palmer and Sorby, 1973). When the right subclavian artery arises anomalously as the most distal branch of the aortic arch, the technique is modified to include catheterization of the aberrant artery and of the right common carotid origin. The site of the origin of the right vertebral artery is therefore clearly demonstrated.

An origin of the right vertebral artery from the right common carotid artery has been demonstrated in three patients in the past three years. In all cases, there was an anomalous right subclavian artery.

The purpose of this communication is to describe the three cases, discuss the significance of this anomaly and suggest that it occurs more commonly than previous literature would indicate.

CASE REPORTS

1. *Female, aet. 42*

Referred because of a single episode of expressive dysphasia of several days duration. Neurological examination normal. Angiography: smooth, atheromatous plaque in the left internal carotid, anomalous right subclavian, anomalous right vertebral (Fig. 1).

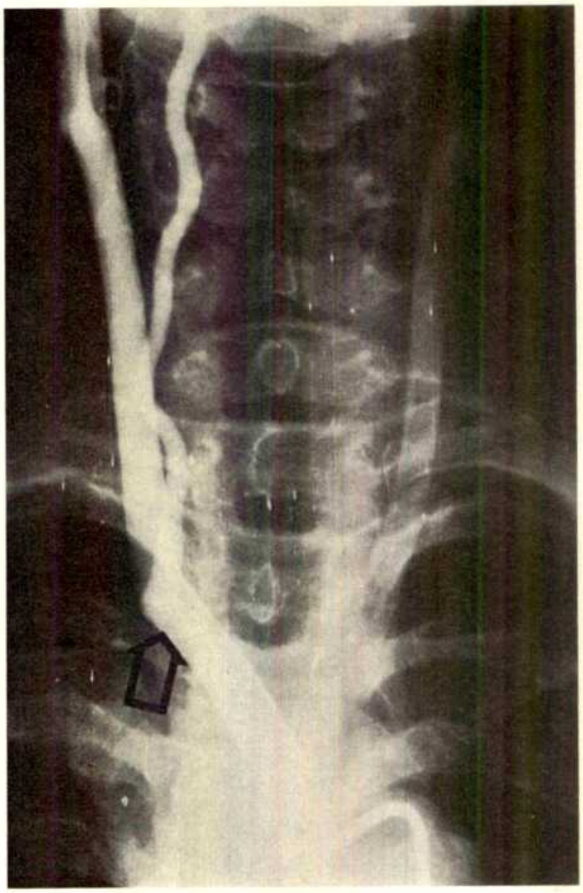

FIG. 1. *Case 1.*

Showing origin of aberrant vessel.

2. *Female, aet. 68*

Presented at another hospital with amaurosis fugax and episodic hemiparesis. Direct carotid angiography demonstrated right internal carotid stenosis and endarterectomy was performed. Symptoms disappeared but persistence of a left carotid bruit five months later led to admission for angiography with a view to further surgery. Angiography: left internal carotid stenosis, aberrant right subclavian artery, common carotid origin of the right vertebral (Fig. 2).

3. *Male, aet. 28*

Referred for angiography during investigations for epilepsy of recent onset. No neurological signs. Angiography aberrant right subclavian, common carotid origin of right vertebral.

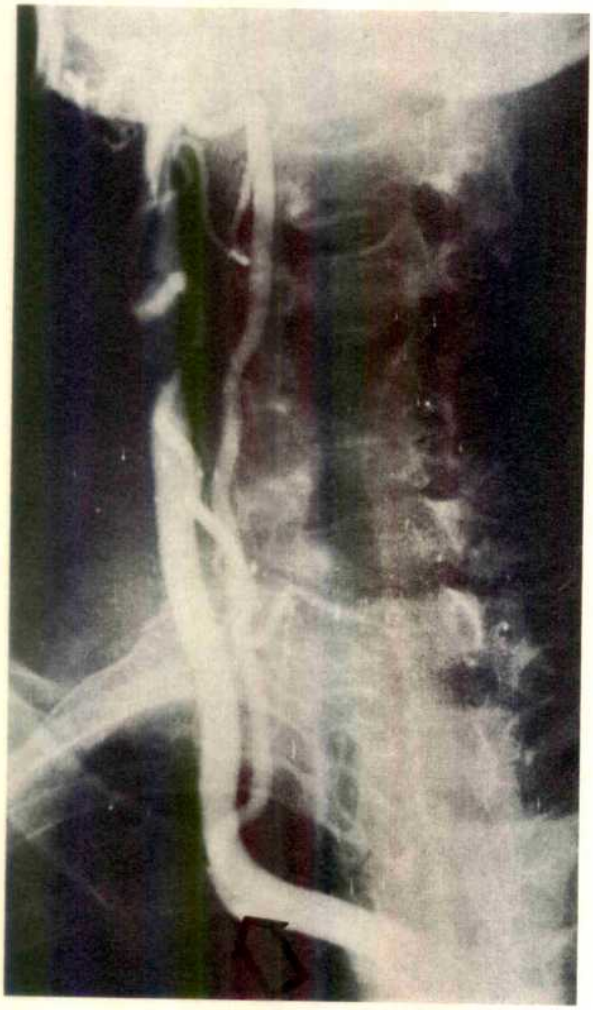

FIG. 2. *Case 2.*

DISCUSSION

Origin of the right subclavian artery from the aortic arch distal to the left subclavian has an incidence of 1–2% in large series (Sutton and Davies, 1966). It is due to involution of the fourth right aortic arch instead of the normal involution of the eighth segment of the right dorsal aortic root (Barry, 1951).

Descriptions in the anatomical literature indicate that the aberrant right subclavian artery gives origin to the right vertebral artery in the majority of instances. This indicates embryogenesis of the vertebral artery from the sixth intersegmental artery. There have also been rare anatomical descriptions of the right vertebral artery arising from the common carotid in the presence of an aberrant right subclavian artery (Chanmugam, 1936; Goldbloom, 1922; Iyer, 1927; Windle *et al.*, 1928). In this situation, the vertebral arteries embryogenesis has been from the third, fourth or fifth intersegmental artery.

Review of the available literature for angiographic descriptions of this anomaly revealed only the two cases of Bernardi and Dettori and single cases illustrated by Newton and Mani (1974), Stein *et al.* (1963) and Tonnis and Schiefer (1959).

Experience of three cases within three years suggests that common carotid origin of the right vertebral artery may be more common than the previous literature suggests. During this period, there were performed approximately 1,700 angiographic examinations at which the presence of such an anomaly would have been detected. This suggests an incidence of approximately 0.18%. The incidence of distal aortic arch origin of the right subclavian artery was 1.1%. In this series, therefore, carotid origin of the right vertebral artery occurred in 17% of subjects in which the right subclavian artery arose as the distal branch of the aortic arch. The relatively high incidence reported in this series, is probably due to the use of selective angiographic techniques. The increasing use of selective methods should lead to demonstration of further examples.

The apparent rarity of this finding, makes three cases worthy of report. However, the presence of this anomaly has certain practical applications which merit consideration:

(1) In the angiographic assessment of cerebrovascular disease, the presence of an aberrant right subclavian artery indicates modification of technique so that the anatomy of the right vertebral artery can be clearly delineated.

(2) Right brachial or transaxillary angiography may fail to demonstrate the right vertebral artery. The presence of this anomaly must then be excluded by alternative techniques.

(3) The surgeon employing by-pass techniques or carotid clamping should be aware of the presence of this anomaly so as to avoid inducing vertebrobasilar ischaemia. Case 2 in this series, had endarterectomy with clamping of the common carotid without complications.

(4) It should be possible to catheterize the anomalous vertebral artery in order to study the intracranial vertebro-basilar circulation. This was not required or attempted in any of the three cases in this series.

(5) Bernardi and Dettori (1975) hypothesize that such anomalies of origin "may favour cerebral disorders because of alterations in the cerebral

haemodynamics". There was no evidence for this in the present cases. However, the significance of atheromatous lesions in the cephalic circulation must always be assessed with regard to variations in calibre, origin and distribution of individual vessels. Atheromatous disease of the proximal common carotid artery might be considered of more haemodynamic significance in the presence of this anomaly.

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Book review

Angiography of posterior fossa tumours. By Samuel M. Wolpert, pp. 238, illus., 1976 (New York, Grune and Stratton Inc.), £12·20.

The simplicity and accuracy of computed tomography has largely relieved the radiologist of the challenge of diagnosing from the minutae of posterior fossa angiograms. However, many surgeons still prefer to map the vascular anatomy adjacent to a tumour prior to resection, especially in anteriorly situated extra-axial lesions.

The accurate interpretation of these angiograms is still sometimes crucial in determining the origin of a tumour.

This small volume presents a simple but comprehensive account of normal vertebral angiography and of the pathological displacements caused by tumours in the various possible situations. The relationship of vessels to normal posterior fossa structures and those displaced by mass lesions are beautifully illustrated by coloured line diagrams and well chosen radiographs.

Chapters on the clinical features and pathology of tumours by Dr. Bennett Stein will be especially useful to those commencing the study of the neuro-sciences. The references are up to date and the index is comprehensive. The book is recommended as an excellent introduction to the subject.

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1977, *British Journal of Radiology*, *50*, 188–194

Medical imaging by NMR

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Abstract

Application of the new nuclear magnetic resonance (NMR) method of fast scan proton imaging is described. Cross sectional proton scans of a human finger *in vivo* are measured and reveal considerable anatomical detail, particularly of the soft tissue regions. Imaging of tumour tissue is also briefly discussed.

During the past few years new techniques have been developed in nuclear magnetic resonance (NMR) which make it possible to form two dimensional cross-sectional images related to the distribution of protons in biological structures (Hinshaw, 1974a&b, 1976; Kumar *et al.*, 1975; Lauterbur, 1973, 1974; Mansfield and Grannell, 1973, 1975a). The methods are non-invasive and of low radiation hazard and could therefore have some clinical value in medical diagnosis. The first crude medical picture of a human finger taken *in vivo* (Mansfield *et al.*, 1974; see also Mansfield and Grannell, 1975b) relied on a slow and inexact imaging method based on reconstruction from a number of projection absorption profiles. Only the gross outline with no internal detail was revealed.

Recently we introduced a new imaging technique which does not depend on reconstruction from projections (Garroway *et al.*, 1974). It relies on selective irradiation of the specimen in switched magnetic field gradients. In the fast scan adaptation of this method (Mansfield *et al.*, 1976) the mobile proton spin density is obtained directly, line by line across the specimen cross-section. Since this work, the apparatus and display have been considerably improved (Baines and Mansfield, 1976) thus enabling us to produce reasonably detailed pictures of a human specimen *in vivo*.

In this paper we wish to report new results obtained with live fingers, particularly with reference to the anatomical information obtained by NMR imaging in normal tissue. Brief reference will be made to imaging of tumour tissue, though we hope to present a more detailed discussion of this aspect of imaging elsewhere.

Principle of operation

The study of structure in materials cannot ordinarily be attempted with conventional NMR techniques. This is because NMR measures frequency differences or magnetic field variations and each piece of resonant material in a specimen is not uniquely defined magnetically. However, by using a combination of switched linear magnetic field gradients plus selective irradiation of the sample, it is possible to uniquely assign a frequency to a particular point in the specimen. The NMR signal coming from a localized region of the sample is directly related to the mobile proton density at that point. By mobile protons we have in mind those contained in the free or nearly free water, fat or oil distributed throughout the soft tissue regions of the specimen. Bone structures, therefore, which contain relatively few mobile protons, are generally detectable through their lack of signal, while tumours and other soft tissues give strong signals. This behaviour contrasts with that of conventional X-rays which are scattered only rather weakly by protons and so usually give pictures for soft tissue regions with relatively poor definition.

Method

The specimen is placed in a large static magnetic field B which polarizes all nuclear spins. (Since biological tissue contains 75–80% by weight of water we are particularly interested in the proton spin

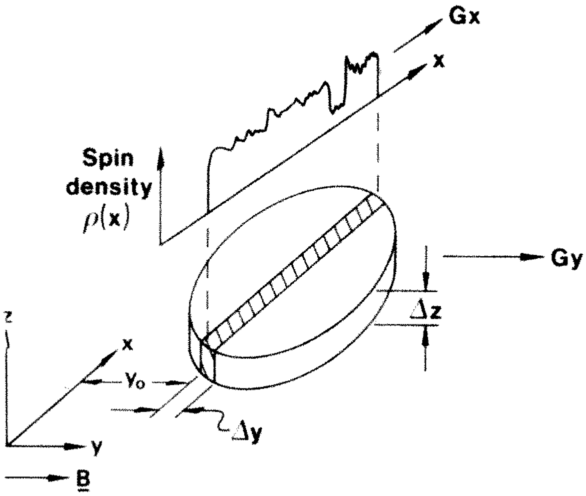


Fig. 1.

Sketch illustrating the principle of line scanning by selectively irradiating a narrow strip within an isolated slice of magnetization.

magnetization, though one could with less sensitivity observe other nuclei.) In addition to this field, switched linear magnetic field gradients are applied along two (or three) principal coordinate axes. We first consider a thin disc or slice of magnetization of thickness Δz within the specimen. Such a slice is sketched in Fig. 1 and is, of course, part of an extended specimen along the z axis.

The field gradient G_y alone is switched on and the spins within the narrow strip Δy at y_0 are selectively excited by applying a "tailored" r.f. pulse to the specimen. The tailoring of the pulse consists of shaping the r.f. envelope such that its spectral distribution is confined to a narrow band of frequencies. A square unshaped pulse, by contrast, has a sinc function frequency spectrum with a width characterized by the inverse pulse length but with extensive sidebands. The r.f. components of the tailored pulse interact with spins in a narrow strip (shaded strip of Fig. 1). This interaction is brought about because the spins within the disc of material have a range of nuclear Larmor frequencies through the action of the linear magnetic field gradient G_y. Thus only those spins within the shaded strip, which have the right Larmor resonance frequency, can respond to the selective r.f. pulse.

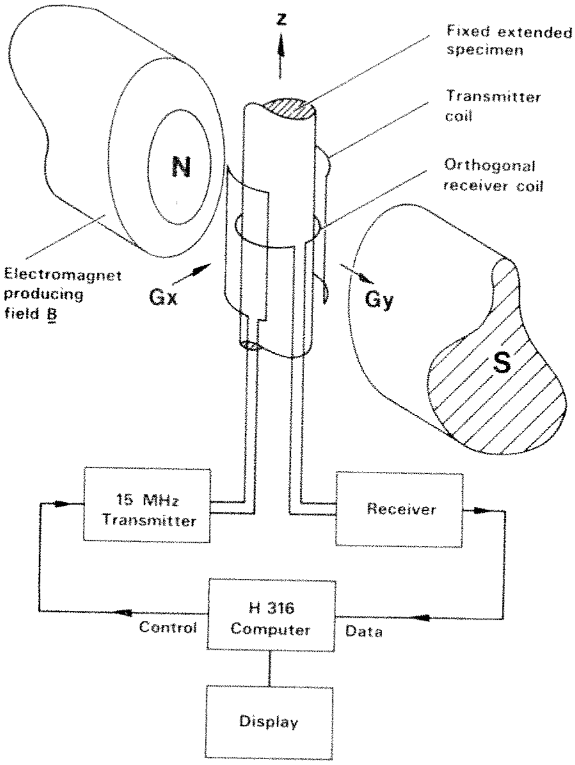


Fig. 2.

Simplified representation of the 15 MHz NMR imaging apparatus. The field gradient coils producing G_x and G_y are not shown.

Immediately following this selective excitation pulse, the field gradient is switched from G_y to G_x and the spin response or free induction decay (FID) signal is recorded and Fourier transformed. For a narrow strip (Δy small) at position y_0 in either a thin slice (Δz small), or for a sample with cylindrical symmetry, this Fourier transformed signal is directly proportional to the proton spin density $\rho(x, y_0)$ along x. The transformed signals for each strip of the specimen are used to modulate the spot intensity of an oscilloscope in a television raster display to form a cross-sectional picture of the object. The display employs a 16-level linear grey scale covering the intensity range black for zero signal to white for high spin density (Baines and Mansfield, 1976).

The initial specialization to a layer or plane can itself be achieved by a selective irradiation procedure in a third field gradient G_z. In these experiments, however, specialization to a layer is achieved simply by relying on the receiver coil geometry. This is a flat coil of 2 cm diameter and our experiments show that most of the received signal comes from a layer approximately 8 mm thick.

A simplified diagram of the imaging apparatus is shown in Fig. 2. The 15 MHz r.f. excitation pulses

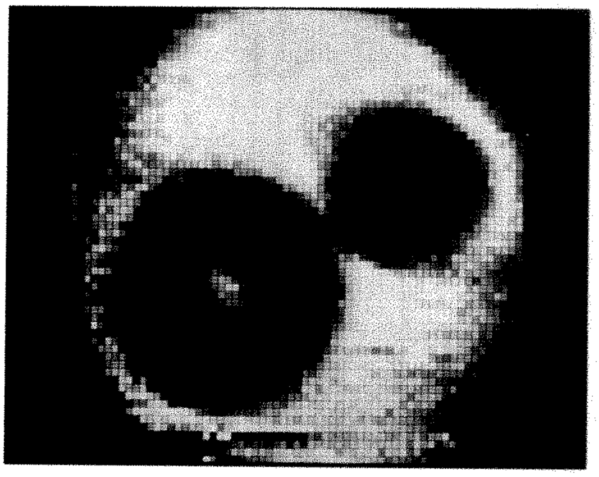


Fig. 3.

Cross-sectional proton scan of a phantom filled with mineral oil (see text for details). The time to produce this picture was 40.5 min. The full picture size slightly exceeds a 64×64 data array, thus squaring off the circular edges. The missing data were not lost but overflowed into the other quadrants of a 128×128 data array. The field gradients were $G_x = 0.69\ G\ \text{cm}^{-1}$ and $G_y = 0.86\ G\ \text{cm}^{-1}$. Each line of the picture was averaged 128 times.

are fed from the transmitter to a pair of cylindrical Helmholtz coils (Ginsberg and Melchner, 1970) surrounding the sample as shown. The peak pulse power was 1.0 watt and the pulse duration 7.4 msec. The production and shaping of the pulses, switching of the field gradients, data acquisition, Fourier transformation and data display are all performed on-line with a Honeywell H316 minicomputer. A more detailed description of the apparatus and the method is given by Mansfield *et al.* (1976). Placing the finger in the receiver coil was found to increase the received noise through the antenna action of the body. However, we found that simply holding an earthed sheet with the free hand reduced the pick up. No other special precautions were taken to shield the receiver coil against induced noise.

RESULTS

Phantom test

Figure 3 is a cross-sectional picture of the proton distribution of mineral oil in a phantom object and illustrates the spatial resolution obtainable in the present line-scan imaging experiments. The sample consisted of a thick-walled 1.4 mm bore glass capillary tube and a solid circular glass rod immersed in mineral oil, the whole being contained in a circular cross-section glass test-tube of inside diameter 14.6 mm. This picture and all biological pictures presented in the next sections are made up from 64 × 64 point arrays.

A linear grey scale wedge is added to later pictures to aid intensity comparisons; however, for precise measurements actual data can be output numerically.

Spin-lattice relaxation effects

We assume here that the local spin magnetization at coordinates x, y in a given plane z is destroyed following one selective excitation pulse, but recovers exponentially, through a single simple spin-lattice relaxation process in a characteristic time $T_1(xy)$. Thus the effective spin density $\rho(xy\tau)$ observed in these images depends on the time delay τ between successive excitation pulses according to the relationship $\rho(xy\tau)=\rho(xy)[1-e^{-\tau/T_1(xy)}]$. That is to say, it is possible for localized regions of the specimen to give a picture brightness which is less than the localized spin density would suggest; for example, if the ratio $\tau/T_1(xy)$ is small. We refer to this effect as spin-lattice relaxation time discrimination and most of the intensity variations between tissue types seem to be attributable to this effect rather than to real density variations, though if present, these too will aid picture contrast.

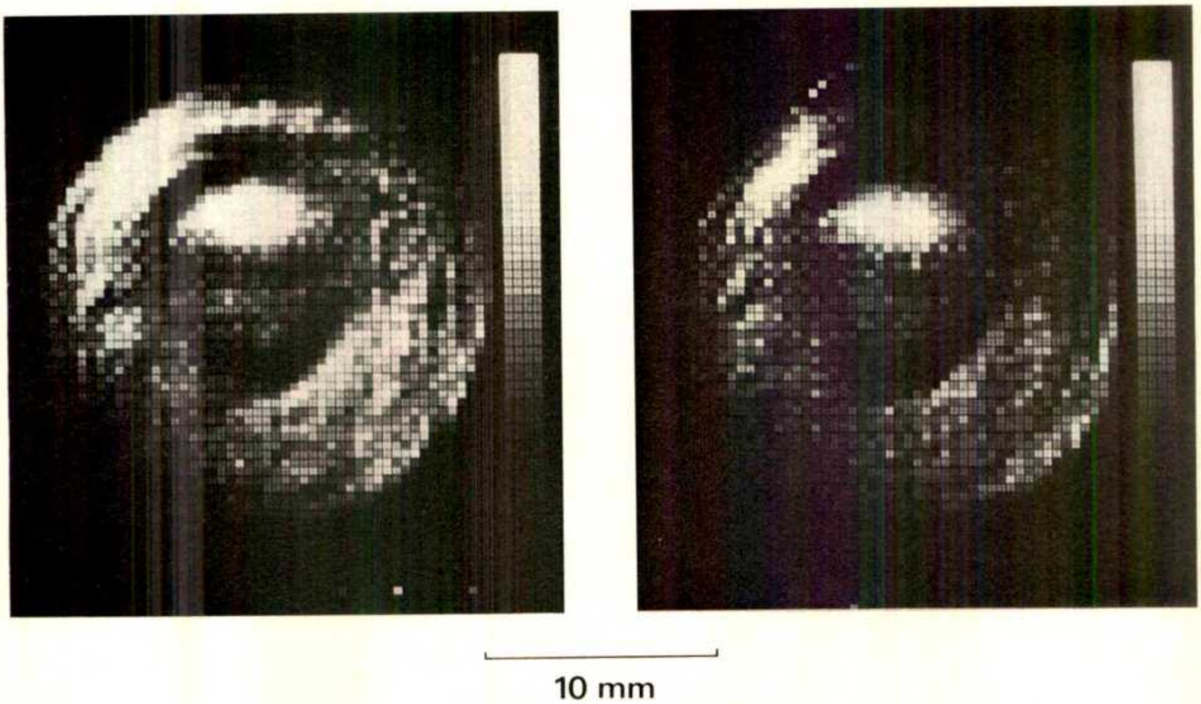
The variations in $T_1(xy)$ within a specimen are a reflection of the variations of both the mobility of the free water, fat or oil and the concentration of dissolved minerals, nutrients, etc., characteristic of the various tissues.

Finger images recorded in vivo.

A number of cross-sectional proton scans have been produced at various positions along the right hand third digit of AAM. We have found that quite good discrimination between the various tissues can be obtained using a delay of 0.5 sec. Similar results and discrimination were found with the finger of another subject (PM).

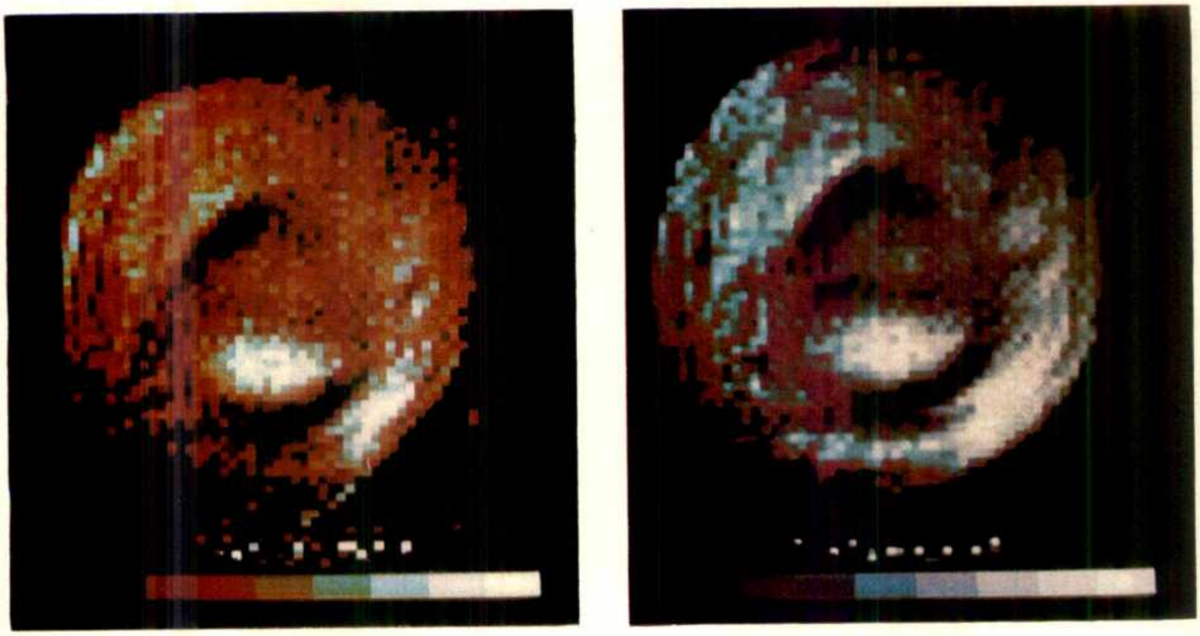
Two scans midway along the mid-phalanx of AAM's third right hand digit are shown in Fig. 4 and correspond to cross-sectional views looking into the end of the digit. The dorsal plane passes through the top and the palmar plane through the bottom of each picture. The delay in Fig. 4A was 0.5 sec. Each line of this picture was averaged 48 times. The final picture took 23 mins to produce. Figure 4B is a proton scan of the same cross-section as 4A, but with the delay τ reduced to 0.3 sec. This picture took 15 min. to produce. The irradiation gradient G_y was 0.41 G cm^{-1} and the read gradient G_x was 0.34 G cm^{-1} for both pictures. Figures 5A and B are colour representations of the data of Figs. 4A and B. The data are presented through a window comprising eight distinguishable colours corresponding to eight out of the original 16 data levels. In order to give easier discrimination the window base level and the colour scales were set in each case to maximize colour contrast between data levels. Figure 6 is a sketch traced off Fig. 4A showing more clearly the anatomical details that we have been able to recognize (Kaplan, 1965; Landsmeer, 1976). (Inevitably some clarity is lost from these pictures in the photographic reproduction.)

Strong signals are received from the skin and subcutaneous areolar and fibro-fatty tissue giving the general outline of the mid-phalangial cross-section. The bone tissue shows as a dark ring surrounding the bright zone produced by strong signals from the marrow region. Immediately below the bone is a second dark ring structure of the fibrous flexor tendon sheath. Within this and slightly brighter are the central flexor profundus and the two unresolved components of the flexor sublimis tendons (flexor digitorum superficialis). Above the bone towards the dorsal plane is a dark horizontal line corresponding to the unresolved mid- and lateral bands of the mid-phalanx extensor tendons. Figures 4B and 5B show the same general characteristics as 4A and 5A, but the



A FIG. 4. B

Cross-sectional images of a finger obtained *in vivo* by NMR (see text for full details).
(A) delay $\tau = 0.5$ sec. (B) delay $\tau = 0.3$ sec.



A FIG. 5. B

Colour versions of the finger images shown in Figs. 4A and B.
(A) The eight colours black through to white correspond to data levels 6–13. The delay time $\tau = 0.5$ sec.
(B) The eight colours black through to white correspond to data levels 2–9.
In both pictures, data falling outside the window limits are presented as all black or all white as appropriate.

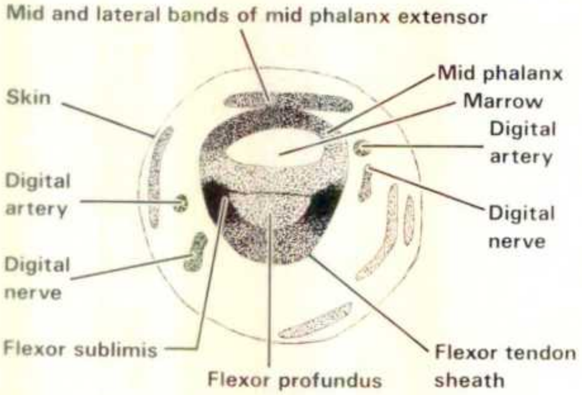


FIG. 6.

A reduced tracing from Fig. 4A showing the recognizable anatomical detail that we have been able to obtain from it.

overall brightness and level of discrimination of the black and white image is reduced with the shorter delay. Differentiation of the flexor profundus from the periosteum and chiasma tendinum are less pronounced indicating that the T_1 of the flexor profundus is of the order of 0.3 sec. The marrow region, on the other hand, remains quite bright. This suggests a T_1 much less than 0.3 sec.

The digital arteries and nerves are just resolved in Figs. 4A and 5A and their positions sketched in Fig. 6. The fact that one can distinguish the arteries from the surrounding tissue means that, with higher resolution or with larger blood vessels in other parts of the anatomy, NMR imaging offers the possibility of making direct blood flow measurements. The principle of such measurements depends on the replenishment of spin saturated blood caused by flow of fresh polarized (unsaturated) blood into the sample coil region, thus producing an apparent reduction in the spin-lattice relaxation time of the blood directly related to its flow rate. Slight modifications to the imaging method described would be necessary for such measurements.

Also apparent in these pictures are darker sliver-like concentric regions or pockets as indicated in the sketch. We ascribe these to discontinuous regions

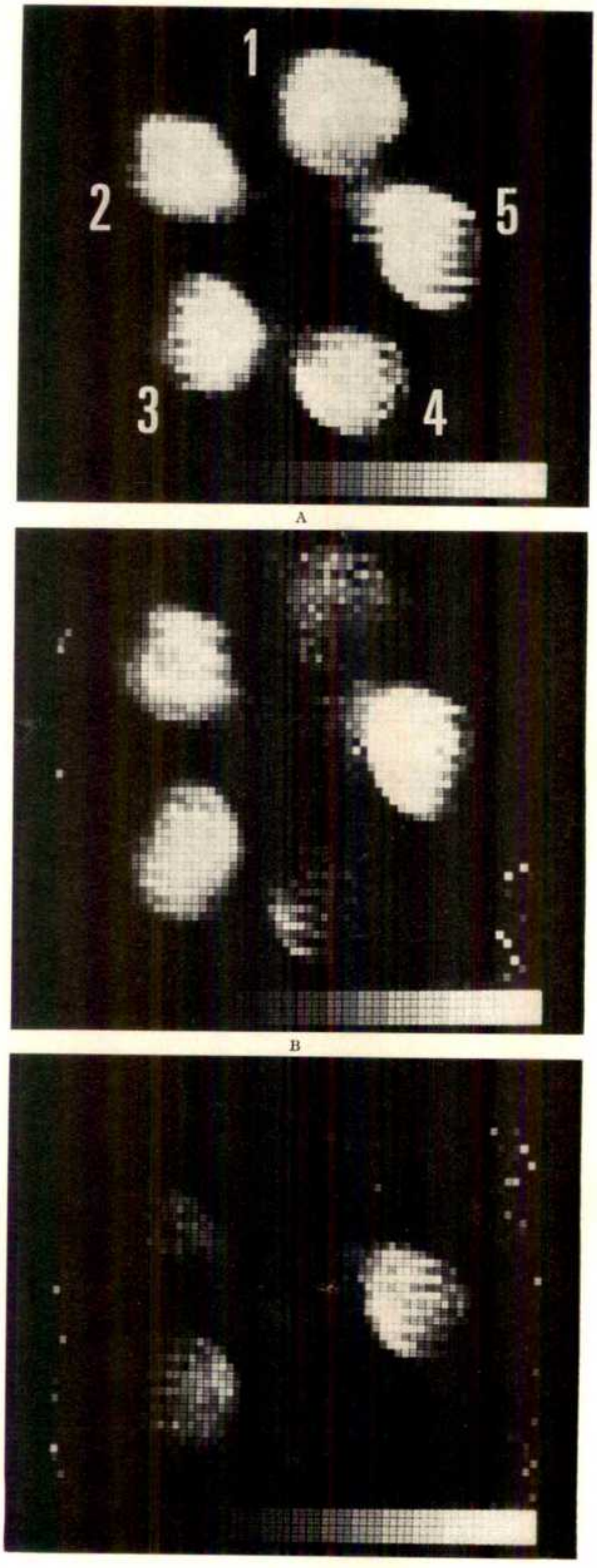


FIG. 7.

Proton scans showing spin-lattice relaxation time discrimination of images obtained from excised rat specimens of normal and malignant tissue. The tissue was contained in 3 mm glass tubes labelled as follows: 1. hepatoma (D23); 2. normal skin tissue; 3. liver; 4. sarcoma (MC7); 5. water control. The specimens in each picture are the same but the delay time τ was varied: (A) $\tau=1.2$ sec; (B) $\tau=0.67$ sec; (C) $\tau=0.37$ sec.

within the fibro-fatty layer which could be either variation in fibro-fatty content or branches of digital nerves or blood vessels. Adipose layers are likely to have a shorter T_1 (Hollis *et al.*, 1975) and would thus appear as bright regions. It would seem from Fig. 4B that these regions, as with other parts of the finger, owe their contrast in the NMR image principally to localized T_1 variations rather than to significant spin density variations.

Cross-sectional scans have also been made through the distal phalangial joint and the mid point and tip of the distal phalanx. In all cases the general features as reported here are reproduced, though the distal flexor and extensor tendons are more diffuse at the joint and the bone somewhat smaller in the distal region as expected.

Tissue Types

From the point of view of the present NMR imaging studies, tissue types can be classified by their mobile proton density (in many cases this is essentially the free water content) and spin lattice relaxation time T_1 (see for example Kiricuta and Simplaceanu, 1975; Hollis *et al.*, 1975). If T_1 is similar between two tissue types, one must rely on more accurate measurement of water concentration to differentiate between them. Our measurements are accurate to only one part in 16 (the display range). Lack of computer core has forced us to discard the original information which had an accuracy of 1 in 10^3. Nevertheless, through T_1 differences, striking contrast can be achieved.

Figures 7A–C show a series of NMR images for decreasing delay τ obtained from the same set of excised tissue specimens taken from young normal white wistar rats. The samples were contained in four 3 mm i.d. glass tubes, labelled 1–4 in Fig. 7. As a control the fifth tube, number 5, contained doped water with $T_1 \simeq 100$ msec. Tubes 1–4 contained respectively hepatoma (D23), a sample of normal skin tissue, normal liver and sarcoma (MC7). Samples 2–4 were taken from the same animal. Both animals were injected with 0.5 ml of the anticoagulant heparin. The NMR images were produced within 2 hours of sacrifice. The delay in Fig. 7A was 1.2 sec resulting in no noticeable discrimination between the various specimens. In Fig. 7B, the delay was reduced to 0.67 sec and clear differentiation between the normal and malignant tissues results. The numerical data for this picture show a slight discrimination between the two normal specimens, numbers 2 and 3, and between the two malignant specimens, numbers 1 and 4. Further reduction of the delay time in Fig. 7C reduces the tumour images to almost zero intensity and begins to affect the intensity of the normal tissue images too. According to Damadian (1971) and others (Weissman *et al.*, 1972; Frey *et al.*, 1972), T_1 in malignant tissue is about 1.5 times longer than that of the corresponding normal tissue. In spite of this small factor, strong intensity contrast is possible in our images by adjusting the delay time τ.

Conclusion

We have demonstrated that NMR imaging of fingers *in vivo* is able to produce reasonably clear cross-sectional anatomical pictures in times up to 23 min. No special precautions were taken to clamp the subjects' hand so that blood flow and general movement, at one time considered to be a possible limit to spatial resolution, have not been found to be troublesome. By implication, therefore, we do not anticipate problems in producing cross-sectional images of the limbs and head where movement can be made negligible. Involuntary movements in other parts of the anatomy are likely to be troublesome, however, unless the scan time can be considerably reduced below 23 min. The experiments described produced no sensation in the finger and the mean r.f. power levels used were well below any perceptible heating level.

The results on normal and malignant tissue suggest that tumourous regions of a subject will give good image contrast against a background of normal tissue. This should aid the detection and diagnosis of tumours in cases where there are no obvious geometrical distortions, that is to say in the early detection of cancer.

Our magnet system has restricted the maximum specimen size to a diameter of 2.0 cm. However, we are planning shortly to study much larger specimens at operating frequencies in the range 1–2 MHz using a specially designed low field spherical electromagnet which is under construction.

Acknowledgments

We wish to thank Dr. M. R. Price for supplying the rat tissue specimens and Dr. H. Clow, Mr. P. Walters and the Directorate of the Central Research Laboratories of EMI for producing the colour pictures of our data.

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Book review

Radiosterilization of Medical Products, 1974. Pp.536, 1975 (Vienna, International Atomic Energy Agency), $33.00.

This volume contains the proceedings of a symposium held under the auspices of the International Atomic Energy Agency at Bombay in December 1974. Of the 42 papers presented in eight sessions, the majority are in English, seven in Russian, three in French and one in Spanish.

Three sessions deal with the conditions required for the control of microbiological contamination and the dosimetric problems involved. The effects of radiation on the materials being sterilized are considered in two sessions and an interesting final session is devoted to the types of radiation plant being used, or about to be commissioned, in different parts of the world. Also included is a report by a working party of the IAEA in which are set out revised recommendations for the radiosterilization of medical products.

This book will be useful not only for those involved in the production of sterile medical equipment, but for those wishing to obtain some background in this field.

N. E. GILLIES.

1977, *British Journal of Radiology*, *50*, 195–199

Treatment tolerance and early complications with extended field irradiation in gynaecological cancer

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ABSTRACT

Treatment tolerance and early complications have been analysed in patients treated with extended field irradiation and pelvic irradiation alone. At the Centre Georges-François Leclerc, 126 patients were treated for carcinoma of the uterine cervix and endometrium from May, 1972 to November, 1974. All patients received external irradiation using a 25 MV X-ray beam. Follow-up has been nearly complete in all patients with the minimum follow-up being 15 months and the average 24 months.

Treatment tolerance was approximately the same for all field sizes except when the field was extended to the top of D12. In this situation the patients occasionally required a short rest during their irradiation. The age of the patient was found to contribute significantly to the tolerance, with 70% of the patients who experienced poor tolerance being older than 60 years. Complications were evenly distributed in all catagories of field size and appeared to be affected only by age and previous surgery. Of the patients who experienced complications 68% were older than 60 years, and of the 37 patients who had previous surgery, 32% had a complication. With certain treatment modifications the treatment tolerance and early complications appear acceptable when using extended field irradiation for gynaecological cancer.

In recent years there has been an increasing use of extended field irradiation in the treatment of cancer of the cervix. This type of treatment, although clinically unproven, appears justified with (1) the knowledge of the lymph node involvement in cervical carcinoma (Brunschwig and Daniel, 1962; Chesin *et al.*, 1975); (2) the ability of irradiation to eradicate the disease when it involves lymph nodes (Rutledge and Fletcher, 1958).

The increased use of high energy photon therapy accompanied by the clinical application of radiobiological principles (Wilson and Hall, 1971) allows extended field irradiation to be more easily employed. In order to evaluate critically the benefits derived by a patient from this treatment the survival and local regional control rates must be looked at along with the complication rates. Several articles discuss these clinical problems (Chesin *et al.*, 1975; Fletcher and Rutledge, 1972; Lebanto *et al.*, 1975); however, they have been limited to a small number of patients with a short follow-up which precludes any definite conclusions from being made.

It is the purpose of this retrospective study to analyse the treatment tolerance and the incidence and type of complications following treatment in those patients receiving a minimum of 4000 rad with either extended field irradiation or conventional pelvic irradiation. Several etiological factors (*i.e.* previous surgery and old age) have also been examined to determine what role they may play in the appearance of complications.

At the Centre Georges-François Leclerc, 126 patients with cancer of the uterine cervix and endometrium were treated between May, 1972 and November, 1974 (Table I). All patients have a minimum of 15 months follow-up, while the majority of patients have 24 months follow-up. Previous studies have shown that more than 90% of complications will appear within four to 24 months after the completion of irradiation (Chau *et al.*, 1962).

MATERIALS AND METHODS

All patients under consideration received irradiation as part of the primary treatment plan. Only those patients with squamous or adenocarcinomas are included in this study. Follow up has been conducted in the Department of Radiotherapy of the Centre Georges-François Leclerc and is greater than 95%. Of the 126 patients treated, 111 had carcinoma of the cervix and 15 had carcinoma of the endometrium.

External irradiation was delivered with a 25 MV photon beam and the basic treatment policies governing field size were as follows:

(1) with limited central and pelvic disease and a negative lymphangiogram, conventional 15 × 15 cm anterior–posterior parallel opposed fields are used when whole pelvis irradiation is not planned to deliver more than 4000 rad in four weeks. If more than 4000 rad are planned then 15 × 9 cm lateral opposed fields (box technique) are added for the first 5000 rad. If further external irradiation is given after 5000 rad then reduced anterior and posterior fields are used for the supplemental dose;

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(2) when the lymphangiogram or exploratory laparotomy reveal involvement of the obturator, external iliac, or hypogastric lymph nodes, then anterior and posterior fields (only) are extended to the top of 4th lumbar vertebra and usually measure 19 × 15 cm. In this situation both fields are treated each day with the daily tumor dose being 170 rad and the total tumour dose 4250 rad in five weeks;

(3) when there is involvement of the vagina and the lymphangiogram is negative the anterior and posterior portals will again measure 19 × 15 cm. In this situation the increase in field size is produced by lowering the inferior border to include all of the vagina. Both fields are treated each day, the daily tumour dose being 170 rad and the total tumour dose 4250 rad in five weeks;

(4) when the lymphangiogram or exploratory laparotomy reveal involvement of the common iliac or para-aortic lymph nodes, the anterior and posterior fields are extended to the top of 12th thoracic vertebra and measure approximately 30 × 15 cm. Both fields are treated each day with the daily tumour dose being 170 rad and the total tumour dose 4250 rad in five weeks.

The number of patients in each group is given in Table I.

All patients received intracavitary caesium therapy when it was part of the general treatment plan. The policies concerning the combination of external irradiation and curietherapy have been described previously (Fletcher, 1973). This study attempts to analyse the complications with respect to the field size in those patients whose primary lesion was considered under control at the time of analysis. A correlation between dose, field size, and complications was looked for, but in this series the complications were found to be randomly distributed over the dose ranges used for treatment.

The complications have been evaluated by correlating the clinical examination with the roentgenographic findings. Each complication has been considered independently and there may be more than one complication per patient.

Results

Treatment tolerance

Tolerance during treatment was recorded in all patients and was divided into three degrees:

GOOD—those patients who experienced no weight loss, nausea, vomiting or diarrhoea.

FAIR—those patients who had nausea, vomiting or diarrhoea which was readily controlled with medication.

POOR—those patients who required constant medication during treatment to control severe nausea, vomiting or diarrhoea. In this group the irradiation frequently had to be stopped for a few days in order to allow the patient time to recover.

The analysis shows that 11% (12/111) of the patients with an L5, L5 extended, or L4 field had a poor treatment tolerance whereas, 33% (5/15) of those patients with a D12 field had a poor treatment tolerance (Table II).

The relationship of age to treatment tolerance (Table III) shows that 12/17 patients (70%) who had poor tolerance were more than 60 years old. When tolerance was analysed to evaluate the effect of previous surgery it was found that four of the 37 patients (11%) with previous surgery tolerated the irradiation poorly as compared to three of 89 patients (3%) when there was no previous surgery.

Complications

The complications are listed in Table IV and are considered separately.

TABLE I

Number of patients in relation to field size and previous surgery

Position of field	L5	L5 extended	L4	D12	Total
Field size	15 × 15 cm	19 × 15 cm	19 × 15 cm	30 × 15 cm	
Total patients	60	27	24	15	126
Patients without previous surgery	44	16	18	11	89
Patients with previous surgery	16	11	6	4	37

TABLE II

TOLERANCE DURING TREATMENT IN RELATION TO FIELD SIZE

	Good	Fair	Poor	Total	Percent with poor tolerance
L5 15 × 15 cm	31	22	7	60	7/60 = 12%
L5 ext. 19 × 15 cm	13	11	3	27	3/27 = 11%
L4 19 × 15 cm	17	5	2	24	2/24 = 8%
D12	6	4	5	15	5/15 = 33%
Total	67/126	42/126	17/126	126	

TABLE III

AGE RELATED TO TOLERANCE DURING TREATMENT

Age (years)	< 30	30–39	40–49	50–59	60–69	70 or over	Total
Good	1	5	16	13	15	16	66/126
Fair	1	3	5	9	14	11	43/126
Poor	0	0	1	4	8	4	17/126
Total	2	8	22	26	37	31	126

TABLE IV

NUMBER OF COMPLICATIONS RELATED TO FIELD SIZE

	L5 15 × 15 cm	L5 ext. 19 × 15 cm	L4 19 × 15 cm	D12 30 × 15 cm	Total
Rectosigmoiditis 1°	2	4	0	3	9
Rectosigmoiditis 2°	4	1	2	0	7
Rectosigmoiditis 3°	2	0	0	0	2
Ileitis	2	1	1	0	4
Cystitis	2	1	0	2	5
Vaginal ulcer	1	1	0	0	2
Rectal ulcer	0	0	0	0	0
Fistulae	2	0	0	0	2
Pelvic fibrosis with complications	1	0	1	0	2
Total number of complications	16/60	8/27	4/24	5/15	33/126

TABLE V

NUMBER OF PATIENTS WITH COMPLICATIONS

Position of field	L5	L5	L4	D12	Total
Field size	15 × 15 cm	19 × 15 cm extended	19 × 15 cm	30 × 15 cm	
Total patients with complications	13/60	6/27	4/24	5/15	28/126 = 22%
Complications in patients without surgery	6/44	3/16	4/18	3/11	16/89 = 18%
Complications in patients with surgery	7/16	3/11	0/6	2/4	12/37 = 32%

1. *Rectosigmoiditis or rectitis.* The diagnosis of rectosigmoiditis or rectitis was established by proctosigmoidoscopic examination, barium, enema and clinical examination. This complication constituted the largest number (18 of 33 complications) and was separated into three degrees of severity.

Degree 1—temporary spasms with some bleeding and intermittent periods of diarrhoea. Radiographic examinations showed spasm of the sigmoid, rectosigmoid or rectum without real narrowing. Proctoscopy showed oedema of the sigmoid or rectum. Symptoms eventually subsided with conservative management.

Degree 2—persistant abnormal bowel symptoms for months frequently requiring transfusions. X-rays showed permanent narrowing. Symptoms eventually subsided with conservative management.

Degree 3—severe bowel disorders often presenting as complete obstruction or necrosis necessitating surgical intervention.

The incidence of rectosigmoiditis appeared with approximately the same frequency with all field sizes employed. However, of the 18 cases observed with this type of complication, eight (45%) of the cases had a history of a previous abdominal surgical procedure. When the complications of those patients with previous surgery were analysed in respect to the field size or the severity of the complication no correlation could be made. Therefore, although surgery augmented the incidence of rectosigmoiditis, the severity and relationship with field size remained the same as in those patients without a history of previous surgery.

2. *Ileitis.* This diagnosis was established by radiographic and clinical examinations. The four cases of ileitis occurred in patients treated for endometrial cancer with a history of previous abdominal surgery. No correlation of complication could be made with field size.

3. *Cystitis.* There were five cases of cystitis, all of which healed with conservative medical management. No differences could be noted with field size or history of previous surgery.

4. *Vaginal ulcer, rectal ulcer, fistulae, pelvic fibrosis.* There were six cases in all with these four types of complication. No differences were noted in their occurrence in relation to field size or previous surgery. All cases healed with conservative medical or surgical management.

DISCUSSION

In analysing the possible benefits of extended field irradiation in the treatment of gynaecological cancer, the importance of patient tolerance during irradiation and complications following irradiation assume a major role in the total treatment plan. These factors appear acceptable when one takes advantage of the decreased integral dose associated with using a 25 MV photon beam and the treatment of both fields per day to reduce "the edge effect".

In this analysis the tolerance during treatment was approximately the same for all field sizes except when using the D12 fields. When the fields were extended to the top of D12 the difficulty encountered during treatment occasionally required an interruption of the irradiation in order to allow the patient a short time to recover. The age of the patient also contributed significantly to the tolerance, with 12 of 17 patients (70%) who experienced poor tolerance being more than 60 years old.

The total number of complications was evenly distributed in all catagories of field size (Tables IV and V). Significant is that 23 of the 33 complications were ameliorated with conservative medical management. After varying periods of time in which the

TABLE VI

AGE RELATED TO COMPLICATIONS

Age (years)	<30	30–39	40–49	50–59	60–69	70 and over	Total
Complications	1	4	1	3	9	10	28
Total patients	2	8	22	26	37	31	126
Percent	50%	50%	5%	12%	24%	32%	22%

complications were medically treated, these patients all recovered completely without any symptomatology secondary to the complication.

When looking at etiological factors the importance of age and previous surgery became apparent. Of the 37 patients who had previous surgery twelve (32%) experienced a complication, whereas of the 89 patients without previous surgery 16 (18%) experienced a complication. Nineteen patients out of 26 (68%) were more than 60 years old (Table VI).

In Table IV it appears that most complications occurred when using the 15×15 cm field, but it must be pointed out that of the 13 patients who experienced a complication in this group, eight patients (ten complications) had previous surgery. It must be stressed that although previous surgery could not be correlated with the severity of complications or field size, it was definitely correlated with the appearance of a complication. Another factor which distorts the number of complications with this field size is that, in general, patients with endometrial carcinoma are treated with a 15×15 cm field and these patients are frequently more than 60 years old with a history of previous surgery and significant medical problems. However, when looking at the total group of patients, the severity and duration of the complications in both the surgical and non-surgical groups were approximately the same.

At the Centre Georges-François Leclerc, the following treatment modifications are now used.

(1) When the pelvic dose is equal to or greater than 5000 rad using a 15×15 cm field, a four-field "box technique" is used for the first 5000 rad.

(2) Above 5000 rad, for any field size, a reduction in the field size is made from 5000 to 6000 rad, and a second reduction from 6000 to 7000 rad.

(3) With fields larger than 15×15 cm we treat at 850 rad per week and both fields are treated each day. In these situations the total tumour dose is 4250 rad in five weeks and 5100 rad in six weeks.

(4) When the patient is more than 60 years old or has had previous surgery, the daily tumour dose should be lowered to 170 rad and both fields should be treated per day when the field measures greater than 15×15 cm.

The incorporation of these modifications into the overall therapeutic plan will continue to improve the tolerance and minimize the complications thereby allowing routine use of extended field irradiation in the treatment of gynaecological cancer. By taking advantage of high energy photon beams and by treating both fields each day the full potential of extended field irradiation can be realized in improving survival statistics and local and regional control rates in the treatment of cancers of the cervix and uterus.

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The application of the "ten-day rule" in radiopharmaceutical investigations

A report of a working party of the M.R.C. Isotope Advisory Panel

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The working party was formed to advise the Medical Research Council's Isotope Advisory Panel on the application of the "ten-day rule" to those individuals undergoing investigations with radiopharmaceuticals. As many of the applications of the use of radiopharmaceuticals are dictated by requirements of clinical research rather than patient management the working party found it necessary to classify the various groups of individuals to whom their recommendations might apply.

Classification of patients

The working party considers that subjects who are investigated using radiopharmaceuticals may be classified in three groups.

(a) Patients and other subjects who are asked to volunteer as controls for research studies.
(b) Patients on whom research investigations are being conducted which are relevant to their clinical condition but which are not strictly necessary for their management.
(c) Patients in whom investigations are required for their proper management.

The majority of patients who are investigated in hospitals are in group (c) and for these the criteria for the limitation of dose were those given in Publication 17 of the International Commission on Radiological Protection entitled "Protection of the Patient in Radionuclide Investigations" (1971). The working group considers that the WHO/IAEA report in 1973 (WHO/RHL/73.1) on "The Use of Ionizing Radiation on Human Beings for Medical Research including the use of Radioactive Materials", is useful in defining the acceptable dose levels in groups (a) and (b). The latter report has subsequently been abstracted in the *B.I.R. Bulletin* (1975).

The "Ten-day rule"

In paragraph 76 of the "Recommendations of the International Commission on Radiological Protection", published in *I.C.R.P. Publication 9* (1966), the Commission "emphasises that the possibility of pregnancy must be taken into account by the attending physician when deciding on radiological examinations that involve the lower abdomen and pelvis of women of reproductive capacity. The Commission also wishes to point out that the ten-day interval following the onset of menstruation is the time when it is most improbable that such women could be pregnant. Therefore, it is recommended that all radiological examinations of the lower abdomen and pelvis of women of reproductive capacity that are not of importance in connection with the immediate illness of the patient, be limited in time to this period when pregnancy is improbable. The examinations that it will be appropriate to delay until the onset of the next menstruation are the few that could without detriment be postponed until the conclusion of a pregnancy or at least until its latter half." Advise on the way of implementing the ten-day rule in X-ray departments has been given by the Royal College of Radiologists (1976).

The application of this "ten-day rule" in relation to the use of radiopharmaceuticals is not so simple because the total radiation dose is received over a time given by the effective life of the radiopharmaceutical in the organ, which may be a substantial part of or even longer than the menstrual cycle.

The gonad doses received from many of the X-ray examinations of the pelvic region are in excess of 100 mrad (in the range 100–1000 mrad) whilst in the majority of investigations with radiopharmaceuticals the dose to the gonads is lower than 100 mrad and is received over a period of time of about 3–4

TABLE I

DOSES TO FEMALE GONADS FROM RADIOPHARMACEUTICAL ADMINISTRATION

Radiopharmaceutical	Gonad dose, mrad/μCi	Typical administration, μCi	Gonad dose from typical administration mrad	Effective half-life
Au–198 colloid	0.25	150	37	3 d
Br–82	2.5 (AWB)	20	50	1.5 d
C–11 monoxide	0.01	5000	60	20 m†
C–11 dioxide	0.02	5000	120	20 m†
Ca–45	0.18	5	1	Long*
Ca–47	3	15	45	4.5 d
Cl–36	0.2 (AWB)	15	3	Long*
Co–57 Vitamin B_{12}	2.1	1	2	Long*
Co–58 Vitamin B_{12}	8.3	1	8	Long*
Cr–51 red cells	0.22	50	11	Long*
Cr–51 denatured red cells	0.2	200	40	Long*
Cs–129	0.23 (AWB)	3000	700	1.3 d†
Cs–131	0.28 (AWB)	1500	420	8 d*
F–18	0.07	8000	560	1 h†
Fe–55	5 (Blood)	20	100	Long*
Fe–59	22	5	100	Long*
Ga–67	0.26 (AWB)	2000	520	2 d†
H–3 water	0.2 (AWB)	500	100	12 d*
Hg–197 chlormerodrin	0.03	100	3	2 d
I–125 iodide	3 (AWB)	10	30	Long*
I–125 Hippuran	0.006	20	0.12	Short*
I–125 HSA	0.62	5	3.1	Long*
I–125 PVP	0.1	50	5	Long*
I–125 Rose Bengal	0.02	350	7	Few d
I–131 iodide	0.3	5	1.5	6 d*
I–131 Hippuran	0.03	10	0.3	Short
I–131 HSA	1.7	5	8.5	6 d*
I–131 MAA	0.3 (AWB)	300	90	12 h†
I–131 PVP	0.4	50	20	6 d*
I–131 Rose Bengal	0.17	200	34	Few d
I–132 iodide	0.2 (AWB)	50	10	2.3 h
In–113m DTPA	0.006 (AWB)	10 000	60	1.7 h†
K–42	1.5 (AWB)	20	30	12 h
K–43	1.1 (AWB)	1000	1100	22 h†
Na–22	17 (AWB)	5	85	Long*
Na–24	2.0 (AWB)	20	40	15 h
P–32	10 (AWB)	100	1000	Few d*
P–32 DFP	100 (Blood)	50	5000	14 d*
S–35	0.013 (AWB)	50	0.7	6 h
Se–75 selenomethionine	10	250	2500	Long *
Sr–85	2.9	40	120	Long*
Sr–87m	0.01 (AWB)	5000	50	3 h
Tc–99m colloid	0.02	2000	40	6 h
Tc–99m complex for renal scintigraphy	0.1	2000	200	6 h†
Tc–99m HSA	0.09	2000	180	6 h†
Tc–99m pertechnetate	0.018	10 000	180	6 h†
Tc–99m polyphosphate etc.	0.018	10 000	180	6 h†
Xe-133	0.004	1000	4	Short

The gonad dose has been used as an estimate of fetal dose during early pregnancy. Data are taken from I.C.R.P. 17, supplemented where necessary with more recent estimates. Where no gonad doses were available the average whole body dose (AWB) was used. All data have been given for intravenous administration (or oral with 100% absorption). Where alternative doses are given in I.C.R.P. 17, in general the most pessimistic has been taken. A "long" effective half-life is used to mean more than a few days, "short" to mean a few hours or less. It is recognized that not all retentions can be characterized by a single exponential process but no changes in category are likely to result from this simplification. Radionuclides are assumed to be in simple ionic form except where otherwise stated.

*"10-day rule" pointless, owing to long effective half-life.

†Typical dose greater than 50 mrad and effective half-life short, so consideration should be given to "10-day rule".

effective half lives. For those radiopharmaceuticals in which this is long compared with ten days the "ten-day rule" is, therefore, of little relevance.

RECOMMENDATIONS

The working party therefore recommends that the implementation of the ten-day rule need only be considered for those patients in groups (b) and (c) in whom radiopharmaceutical investigations are to be undertaken which:

(i) Give gonad doses in excess of 50 mrad, and

(ii) Have effective half lives short compared with 10 days.

The value of 50 mrad was chosen as corresponding to the limit of dose to the total body in category I of the WHO/IAEA report.

The working party prepared Table I which gives, for the activities of radiopharmaceuticals normally administered, the effective half lives and resulting gonad doses. The radiopharmaceuticals to which the above recommendations apply are therefore identified as ^{11}C monoxide and dioxide, ^{18}F, ^{43}K, ^{67}Ga, ^{99}Tc^{m} complexes for kidney scintigraphy, HSA, pertechnetate, polyphosphate and similar bone scanning agents, ^{113}In^{m}DTPA, ^{129}Cs and ^{131}I macroaggregates. When greater activities than considered typical in this report are administered other radiopharmaceuticals will also fall into the above category.

When the administration of therapeutic quantities of radiopharmaceuticals is being contemplated it is particularly important to take into account the applicability or otherwise of the "ten-day rule".

However, in order to keep the radiation dose to the minimum possible for women of child-bearing age who are volunteers ***for research purposes*** (group (a)), we recommend that the "ten-day rule" should be strictly applied for all radiopharmaceutical administrations.

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Book review

Synopsis of Analysis of Roentgen Signs in General Radiology. By Isadore Meschan, pp. 677, illus., 1976 (W. B. Saunders Co.), £17·00.

There are those who like synopses, and those who don't. For those who do, this volume offers a distillate of the already published three volume text by the same author. The author has clearly been at great pains to preserve a balance of aspects and detail covered, and sets out to compile and illustrate the major radiological signs in general radiology, offering methods of classification and correlating them with clinical medicine. There are 677 pages, packed with illustrations and lucid line diagrams usually of high quality. The script and tables are clearly presented and easily readable. There are enough important references quoted to give an adequate start in the pursuit of a subject in depth, without there being a surfeit. Each chapter is concluded with a short series of questions designed to test the assimilation of fact by the reader. The index is generally very well produced.

The book deals in detail with plain film radiology and basic contrast medium techniques such as barium studies and urography. There is scant reference to techniques such as tomography, myelography or arteriography. Topics including scintigraphy, sonography and CT scanning are, by definition, excluded.

The author aims his book at medical students, general clinicians and the younger radiologist requiring a broad purview of the subject. It is this last group that will especially appreciate the book. It will act as excellent illustrated lecture notes, with many basic facts and good clear illustrations and tables. The author is honest to his title and classifies disease according to radiological, not pathological, signs and provides just enough clinical medicine to put them into the context.

One would wish to recommend this book to the new trainee who, having bought a standard text, would find it an excellent companion synopsis. But, as it is by definition rather superficial, it would not substitute for such a standard text. The established radiologist will find it a valuable reference volume for rapidly reviewing the major features of disease outside his usual area(s) of interest. It is a necessary purchase for the libraries of departments dealing with post- and undergraduate tuition.

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1977, *British Journal of Radiology*, *50*, 203–204

The use of thyroid blocking agents

A report of a working party of the M.R.C. Isotope Advisory Panel

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For many years the M.R.C. Isotope Panel has authorized the use of radiopharmaceuticals with the proviso that the thyroid gland be blocked when appropriate. However, the actual procedures or policies to be followed have not been formally stated and the working party was asked to study the present information and to report to the panel.

Investigations involving the administration of technetium 99m

The working party recommends that when activities of technetium-labelled radiopharmaceuticals below 5 mCi are being administered there is no requirement to use a thyroid blocking agent.

Where activities higher than 5 mCi are being administered, thyroid blocking agents should be administered when they do not conflict with the objectives of the test, *e.g.* the visualization of the thyroid. The working party recommends that the blocking agent to be used should be either 50–100 mg of potassium perchlorate administered intravenously at the time of the injection of the radiopharmaceutical or 200–400 mg administered orally half an hour to an hour before the test. There is good clinical experience that would indicate that this procedure is effective and harmless.

For reasons outlined below the administration of perchlorate as a blocking agent seems preferable to the use of potassium iodide or Lugols solution.

Investigations using radioactive iodine

The working party considers that this problem should be sub-divided according to the type of investigation and the radiopharmaceutical used. In all cases, however, the use of potassium iodide or Lugols solution as blocking agents in patients should be carefully considered because of possible iatrogenic effects, the possible need for subsequent thyroid function tests and the questionable efficacy of any particular blocking agent regimen. In geriatric and coronary patients the hazard associated with the administration of such blocking agents may be greater than the radiation hazard caused by not using a blocking agent at all, *e.g.* Denham and Himsworth (1974) have recently drawn attention to the possible danger if hyperthyroidism is induced in coronary patients by the administration of potassium iodide.

RECOMMENDATIONS

(1) *Potassium perchlorate*

Where the use of potassium iodide or Lugols solution is contra-indicated the working party considers that potassium perchlorate would appear to be an acceptable alternative blocking agent at levels of 400 mg per day only if given for a short period of time. Many of the experts who have advised the working party about this subject have reservations with regard to the long term administration of potassium perchlorate in view of the possibility of agranulocytosis. There is, however, only limited information on this subject available.

(2) *Radiopharmaceuticals that are stable in the body and are not metabolised*, e.g. *Hippuran, Rose Bengal*

Present-day quality control in the preparation of radiopharmaceuticals is very good and for these radiopharmaceuticals the presence of any free iodide can be ignored, and, therefore, no blocking agent is required.

(3) *Investigations in which blocking of the thyroid is not required for technical reasons, but is to be used to reduce the radiation dose to the patient*

(a) The first category of these investigations is those in which radiopharmaceuticals having a short biological half life (a few hours) are to be used, *e.g.* investigations using radioactive fats or macroaggregates used for lung scanning. In these cases a single administration of blocking agent is sufficient. The working party recommends that a single oral administration of 60 mg potassium iodide or 400 mg potassium perchlorate is given at the time of the administration of the radiopharmaceutical.

(b) The second category is those investigations in which radiopharmaceuticals having a long effective half life are to be used, *e.g.* ^{125}I fibrinogen tests for deep vein thrombosis. In these cases continuous blocking is required.

The working party considers that 30 mg of potassium iodide daily for the period of the test would be adequate to block the thyroid.

(4) *Complete blocking of the thyroid is required for technical reasons associated with the investigation*

e.g. in labelled protein turnover studies in which it is necessary to get complete recovery of the metabolized radioactive iodine in the urine.

The investigator will have to choose the appropriate level of thyroid blocking, bearing in mind the limitations referred to in a previous section regarding patients with a previous history of thyroid diseases, especially those with cardiac disorders.

The commonly used blocking régime of 60 mg of potassium iodide twice daily throughout the period of the test will undoubtedly achieve the desired objective. However, the work of Ramsden *et al.* (1967) suggests that thyroid uptake can be maintained at less than 1% of the normal with an administration of 35 mg every 12 hours.

Recent studies suggest that if the iodide is given in repeated small doses (*e.g.* in food or drinking water) the amount of potassium iodide may be reduced to 35 mg per day (Wootton and Hammond, 1976).

It should be noted that in this category of investigation the administration of the blocking agent is a requirement of the test rather than of radiation protection, although the dose reduction achieved is desirable.

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Book review

Yearbook of Nuclear Medicine, 1976. Ed. James L. Quinn, III, pp. 380, 61 figs. (Yearbook Medical Publishers; distributed in U.K. by Lloyd Luke (Medical Books) Ltd.), £15·30.

The yearbooks in various subjects will be familiar to most readers. This year's yearbook on Nuclear Medicine follows the usual format of previous years and of the other subjects. The lead article this year concerns the challenge of computerized axial tomography to nuclear medicine imaging. Dr. Michel Ter-Pogossian is an extremely suitable person to write this article since he is involved with tomographic imaging of all kinds. Happily he comes to the conclusion that although CAT is a formidable challenge, nuclear medicine will still be used by exploiting its strength in functional imaging. Interestingly he does not really comment on high resolution ultrasound imaging which perhaps offers more of a challenge in imaging several organs in the abdomen.

The remainder of the volume includes abstracts from the world literature in nuclear medicine. As in former years it is hard to find any important article which is missing. The section on radiochemistry and radiopharmacology is getting longer each year. This year it has been expanded to include articles concentrating on tumour localizing agents which obviously do not fit into chapters concerning specific organs. There have been quite a few new pharmaceuticals developed over the past two years. Their impact on clinical studies is now beginning to become obvious. Whereas previously one had been rather pessimistic about the future of nuclear medicine, equipment having appeared to have reached a plateau, there is no doubt that these new more specific radiopharmaceuticals are producing much better results. Typical examples include new gall-bladder imaging agents labelled with short-lived isotopes and the newer bone scanning radiopharmaceuticals. As might be expected there are several papers on cardiac work discussing the newer ways of imaging myocardial infarction.

As always the yearbook provides an extremely useful and excellent review of the subject of nuclear medicine which can be recommended even to all those with only a passing interest in the subject.

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1977, *British Journal of Radiology*, *50*, 205–207

Technical notes

Test of rare earth oxysulphide intensifying screens

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The introduction of fast tungstate intensifying screens was a remarkable step toward dose reduction in diagnostic radiology (Soila and Suolanen, 1963). Intensifying screens made of terbium activated gadolinium and lanthanum oxysulphides have a higher X-ray absorption and exhibit a larger conversion efficiency from X-rays to visible light than calcium tungstate screens (Buchanan *et al.*, 1972). The use of rare-earth screens thus provides a considerable reduction of radiation dose as compared with conventional screens (Ardran *et al.*, 1975). Different types of rare-earth intensifying screens are available; the physical properties of the screens are well documented (Stevels, 1975). There are, however, few reports on the clinical use of rare-earth screens and possible differences between them and conventional screens in practical work (Evans *et al.*, 1975; Wiljasalo *et al.*, 1975).

Experiments and Results

The resolution capacity of each film–screen combination was tested with an E-plate especially

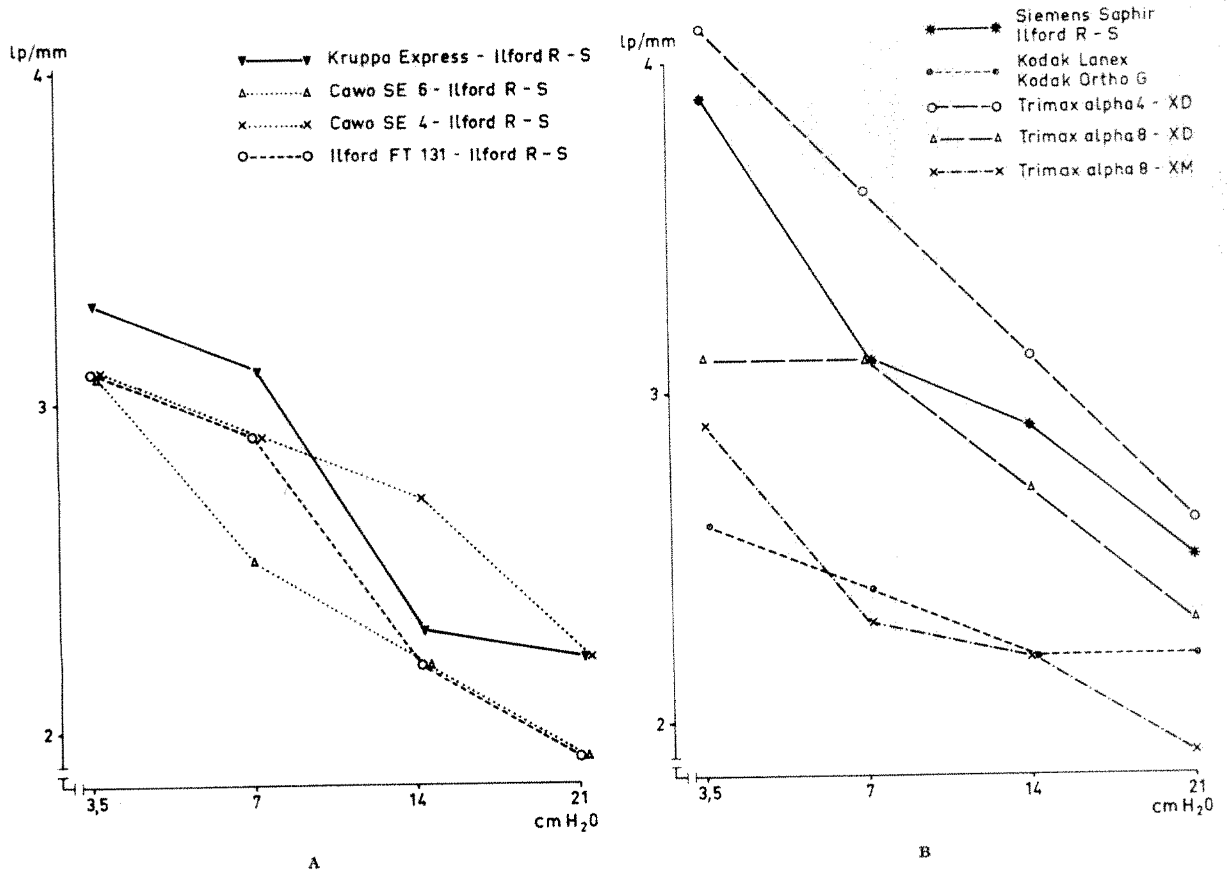

Fig. 1.

Graphs of resolution capacities in line pairs per mm (lp/mm) of (A) fast tungstate and blue light emitting rare earth screens and (B) standard screens and green light emitting rare earth screens below a water phantom of varying thickness.

TABLE I

FILM-SCREEN COMBINATIONS AND CORRESPONDING DOSES AND OPTICAL DENSITIES AT 80 kV USING A WATER PHANTOM 3.5 CM THICK

Screen	Film	Dose at entry surface (mrad)	Optical density (background subtracted)
Kruppa Express (Fast tungstate)	Ilford R-S	30	1.2
Siemens Sapphire (Standard screen)	Ilford R-S	75	1.4
Trimax Alpha 8*	Trimax X M	10	1.5
Trimax Alpha 8*	Trimax X D	20	1.4
Trimax Alpha 4*	Trimax X D	40	1.3
Kodak Lanex*	Kodak O G	20	1.4
Cawo SE 6†	Ilford R-S	15	1.5
Cawo SE 4†	Ilford R-S	20	1.5
Ilford FT 131†	Ilford R-S	15	1.5

* Green light emitting screen †Blue light emitting screen

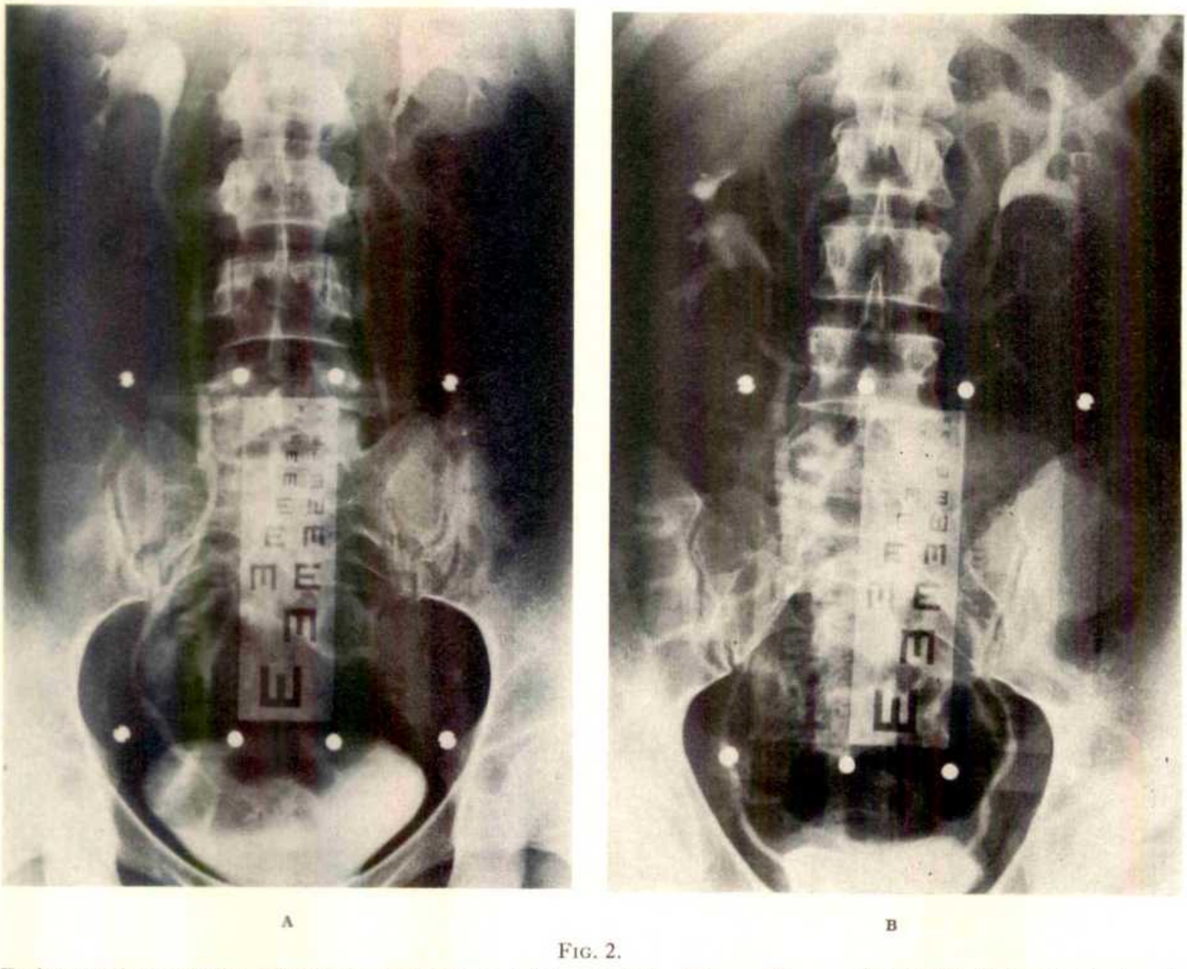

FIG. 2.

E-plate test in urography. (A) Fast tungstate screen and standard film (Kruppa Express, Ilford RS). Patient R.M. (female weight 55 kg, height 165 cm). Skin dose in the primary field from 10 exposures 4.5 rad. (B) Rare-earth screen and green sensitive film (Trimax Alpha 8-XM). Patient E.E. (female, weight 55 kg, height 167 cm). Skin dose in the primary field from 10 exposures 1.5 rad.

designed for mimicking clinical situations (Soila and Tähti, 1965; Laasonen, 1968). The test films were exposed through layers of 3.5, 7, 14 and 21 cm of water, using an X-ray equipment with a 12 pulse generator and electronic contactor. The film-focus distance was 90 cm and the diameter of the focal spot was 0.6 mm. In Table I the tested film-screen combinations are listed. The doses were measured by thermoluminescent dosimeters at the surface of the 3.5 cm phantom and the optical densities were measured with an electronic densitometer. With the addition of every 3.5 cm of water the exposure values were doubled, thus the optical densities were kept within the range of those with the initial water layer throughout the experiment.

The results of the water phantom experiments are seen in Fig. 1. The fastest of the screen–film combinations (Trimax Alpha 8-XM) was used for urography in four patients and the results were compared with four radiographs made with a currently used film–screen combination (Kruppa Express, Ilford R-S). The E-plate was used for estimation of the resolution differences in the same manner as in the water phantom experiment.

No additional films were needed for the test. According to this test the mean resolution capacity was 1.6 lp/mm for both film–screen combinations. An example of the image quality is seen in Fig. 2.

CONCLUSIONS

The best resolution was observed with the Trimax Alpha 4-XD combination. The result was slightly better than with the standard screen–film combination (Siemens Sapphire Ilford RS) but only half the dose was needed. The Trimax Alpha 8-XD combination was only slightly inferior to the standard screen–film combination but only one fourth of the dose was needed. The other rare-earth screen–film combinations had almost the same resolution capacities as the fast tungstate screen–film combination (Kruppa Express, Ilford RS), but they needed one third to two thirds of the dose.

The loss of resolution capacity caused by increasing object thickness was more pronounced in the slow screen–film combinations than in the fast ones.

In a resolution test made during urography no difference between information content provided by Trimax Alpha 8-XM combination or the fast tungstate screen–film combination could be detected. The rare earth screen–film combination reduced the dose to one third. This observation was in accordance with the results from the water phantom experiment.

ACKNOWLEDGMENTS

We are indebted to Messrs. Oy Havemann Ab, Lääketukku Oy, Lääkintäsähkö Oy and Oy Röntgentekno Ab for providing films and screens and to Mr M. Heikkilä, M.Sc. for technical assistance.

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A 10×10 cm photographic cassette for use with gamma cameras and other equipment requiring photographic recording from an oscilloscope screen

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The ideal system for recording images from an oscilloscope has not yet been produced. Polaroid film is probably the most widely used method, but is expensive, has a more limited exposure latitude than transilluminated film, is difficult to demonstrate to a second person because of the surface gloss when viewed by reflected light, and impossible to demonstrate adequately to a larger group. A life-sized picture on X-ray film is larger than is necessary to display the information actually present in a scan, so that detail becomes difficult to distinguish from high frequency noise. It is more expensive than Polaroid, and requires a large storage space.

The 70 mm roll film is popular, but currently available cameras for this size are either expensive motor driven models with many rarely required facilities, or simple film backs designed for professional photographic use, which are difficult to load with the more rigid X-ray films and do not stand up well to the rugged environment of the hospital. Moreover the image obtained is in many cases smaller than ideal. Recently, 5×4 in., Nuclear Medicine film has become available in the United States. It is not yet available in the United Kingdom.

The 10×10 cm (100 mm) cut film is increasingly used in many X-ray departments for photofluorography and copying of full-sized X-ray films. It is the smallest standard size which can be processed through automatic roller-processors without the need of attachment to a leader. The image size which can be obtained is adequate for viewing by an audience in a small seminar or conference room. The film itself is readily available from most X-ray film manufacturers and is the least expensive of the methods discussed.

The 10×10 cm film can be fitted into photographic 5×4 in. double dark slides, but these are not ideal because it is easy to load the film incorrectly so that it falls out when the dark slide is withdrawn, but difficult to load correctly. These objections also apply when 5×4 in., Nuclear Medicine film is used.

The size of image obtained on type 107C Polaroid film, which is approximately $3\frac{1}{2} \times 4\frac{1}{2}$ in., fits conveniently on to 10×10 cm cut film. The majority of manufacturers of the photographic recording equipment used with γ camera oscilloscopes also manufacture an alternative back known as the international "M-size" which can be exchanged with the Polaroid pack holder. No other modification is necessary to the camera. These "M-size" backs will take either 70 mm roll film or 5×4 in. double dark slides.

A modified double dark slide has been designed specifically to take 10×10 cm X-ray film and to stand up to a hospital environment. The prototype has been in use in the medical radioisotope department at the Western General Hospital for some months and has proved entirely satisfactory. It is easy to load even in total darkness, and the film combines the advantages of a display on clear film viewed by transillumination with the facility

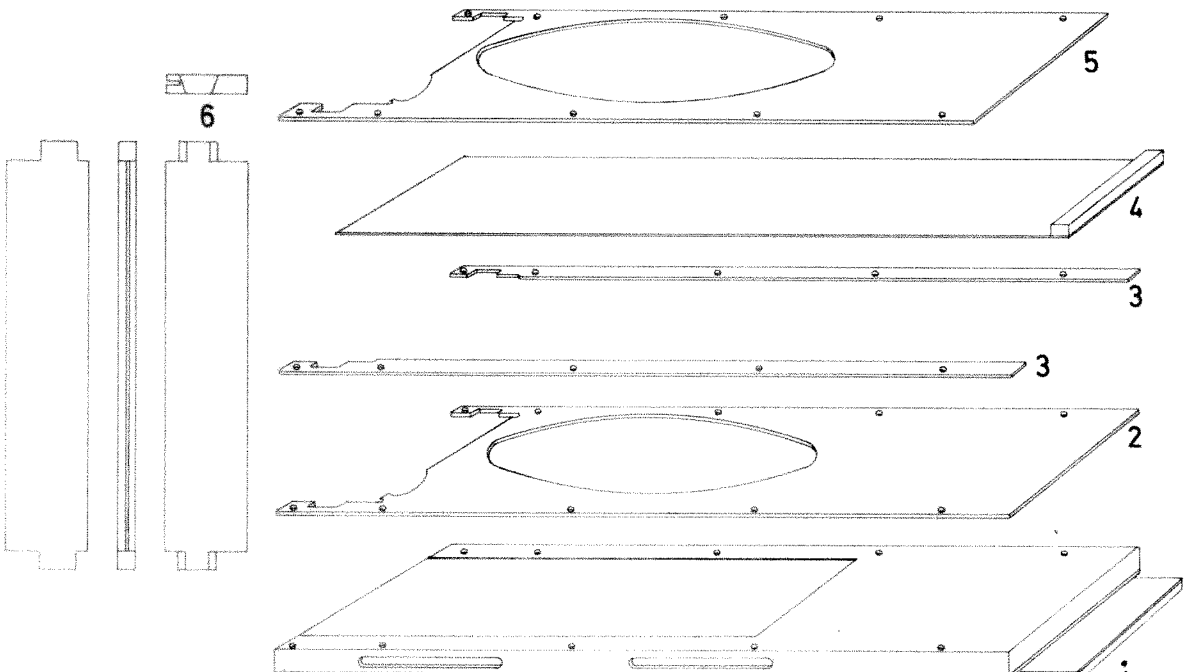

Fig. 1.

Exploded diagram of film holder.

1. Base with recess to receive film. Lower side is shown assembled. 2. Plate with circular aperture to retain film by corners. 3. Spacing strips. 4. Dark slide. 5. Face plate. 6. Flap attached to body (1) by fabric hinge (not shown).

previously enjoyed only with Polaroid of viewing the processed film before the patient is discharged from the department.

The prototype is constructed in aluminium (Fig. 1) although if large scale production were contemplated plastic moulding might prove preferable. It consists of a base (1) 6 mm thick into which is milled a recess just deep enough to take a sheet of 10 × 10 cm film. This base is covered by a thin aluminium plate (2) containing a circular aperture 95 mm in diameter exposing all but the corners of the film. A second similar plate (5) is separated from the first by a pair of thin spacer strips (3) which provide access for a further thin piece of aluminium (4) which acts as a dark slide. One end of pieces 2 and 5 is recessed to allow room for a trap (6) which is opened for removal or insertion of the film. It is attached to the main body by a fabric hinge. A groove in the trap is engaged by the dark slide to prevent it opening inadvertently.

ACKNOWLEDGMENTS

We would like to thank Mr. John E. Pizer of the Department of Medical Illustration for preparing the drawing. Engineering drawings are available on application to L.M.

Visualization of superficial vasculature using a Vidicon camera tube with silicon target

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(Received September, 1976)

Infrared photography has been used by a number of authors in the study of disease (Ronchese, 1937; Massopust, 1948). The technique depends upon the fact that radiation of wavelength 0.7 to 1.2 μm penetrates the skin to a depth of about 2 mm and is absorbed more strongly by blood than surrounding tissues. To avoid shadows, the area to be photographed should be illuminated with diffuse uniform lighting and, since infrared emulsions are sensitive to visible as well as infrared radiation, a filter must be placed over the photographic camera lens. Although infrared photography is in principle a simple technique, it requires careful execution to achieve consistent results. We have found it advantageous to replace the photographic camera by a TV camera with a silicon target Vidicon tube*. As a photosensor, silicon is highly efficient over a broad band of the electromagnetic spectrum including the ultraviolet, visible and near infrared up to a wavelength of 1.2 μm. The system we use consists of an RCA 4532A 25 mm diameter Vidicon type tube employing a silicon-diode array target structure fitted in a modified Link 101 TV camera with a Cosmicar TV lens (25 mm diameter, *f*1 to 1.9). A Kodak Wratten No. 87C filter is used over the camera lens and this modifies the spectral response characteristics of the silicon tube as shown by curve (b) in Fig. 1. The monitor screen can be photographed if a permanent record of the infrared image is required. The system was designed principally for use in the Early Diagnostic Centre (Breast Unit), Royal Marsden Hospital, London, to study superficial breast vasculature in association with thermography (Jones and Draper, 1970), but clearly there are other applications especially in vascular surgery, dermatology and ophthalmology. Figure 2 illustrates a photograph of the infrared image on the TV screen showing subcutaneous superficial vasculature of a heavily pigmented negress.

The system has the following advantages over conventional infrared photography:

(1) Brightness and contrast control of the TV monitor permits visual optimization of the displayed image for a particular field illumination.

(2) Real-time viewing of the superficial vascular pattern allows surface location of blood vessels. Dynamic studies can be carried out with cine-camera or a videotape recorder so that the effect of vasodilatory drugs and other methods of altering blood flow may be studied.

(3) The effect of altering the illumination of the subject can be readily studied and optimum conditions selected. This is particularly advantageous when the camera is used in an operating theatre or clinic. When over-lit, a

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* Available from RCA Electronic Components Ltd.

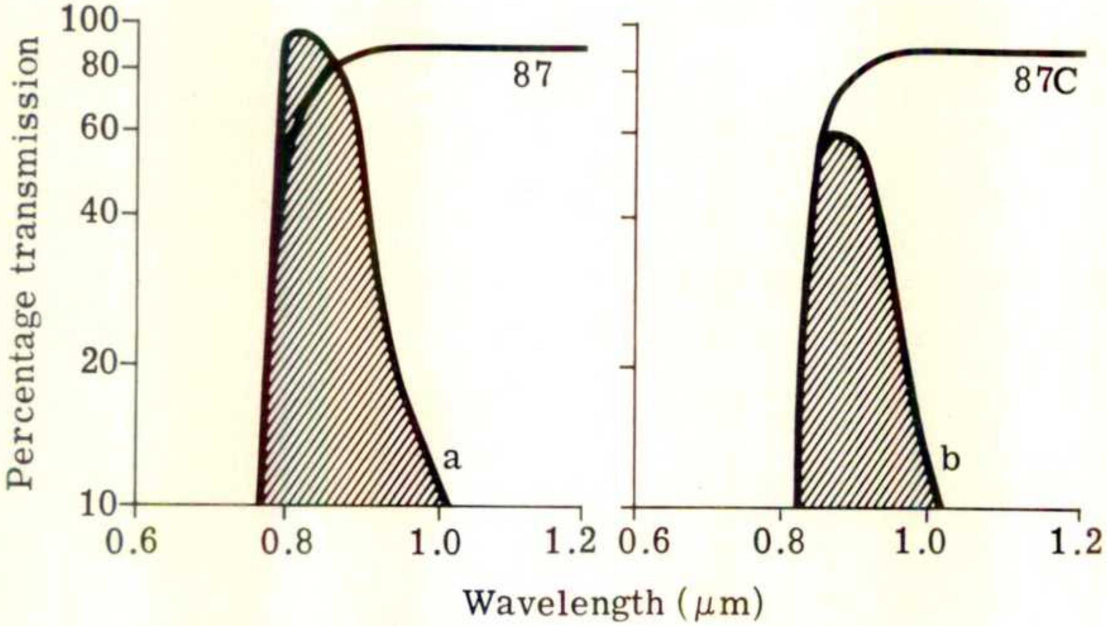

Fig. 1.
Transmission curves for Kodak Wratten filters 87 and 87C. Curves (a) and (b) show the effective spectral response in relative units of RCA silicon tube when used with appropriate filter.

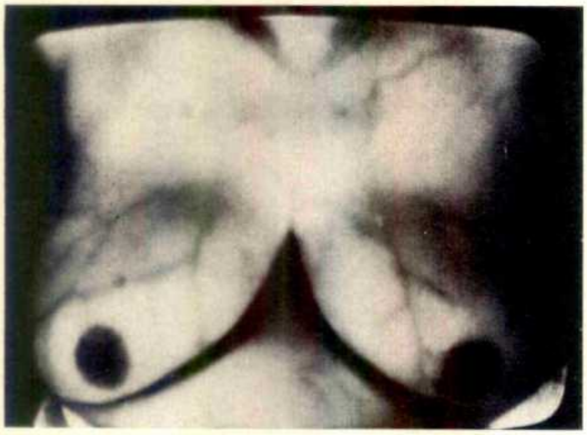

Fig. 2.
Photograph of TV monitor screen showing superficial vasculature of a heavily pigmented negress.

silicon target tube may fail to produce a picture but it will promptly recover when proper lighting levels are restored.

(4) The TV monitor can be sited remote from the camera: this facility is useful for teaching and demonstration purposes.

The silicon target Vidicon system can also be used in situations where visible light is excluded such as patient monitoring in the "dark".

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Technical notes

A method of removal of knotted Headhunter catheter

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Since the introduction in the late 1960s of "Headhunter" catheters, and in particular the S-shaped (Type IV) for the catheterization of carotid and subclavian arteries, knotting has been reported when using a 7-French (Gletne and Guckman, 1971), and less frequently with 8-French catheters (Chinichian *et al.*, 1972).

A useful practical paper on the non-surgical manipulation and reduction of knots was written by Young and Maurer (1970). These authors used a method of fixing the distal tip of the catheter between the orifices of the left carotid and subclavian, so that when the catheter is advanced this loosened and enlarged the knot until the tip was within the loop. Then, on gentle withdrawal and re-insertion of the guide wire, there was sufficient straightening to eliminate the knot.

These authors stressed the need for early recognition of this complication by using fluoroscopy control and the use of 8-French rather than 7-French catheters, as the incidence is then very much less common.

We have recently encountered this complication (Fig. 1A) and without previous knowledge of the paper by Chinichian *et al.* (1972) successfully reduced the knot in the manner they described. We would therefore like to draw attention to this useful technique.

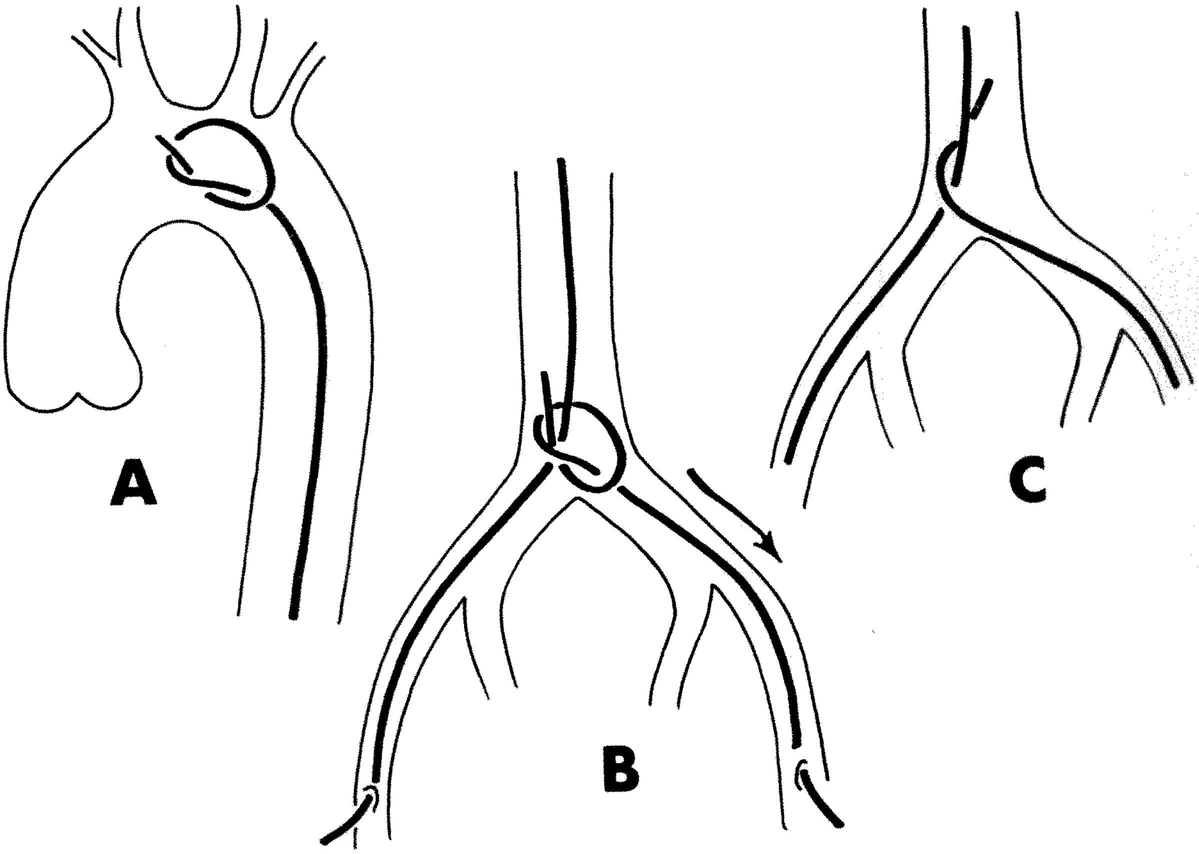

FIG. 1.
(A) Orginal position of the knotted catheter.
(B) Withdrawal of the knotted catheter to the line of the bifurcation of the aorta, followed by introduction of a second catheter.
(C) Unfolded knot.

TECHNIQUE

With the formation of a knot attempts should be made to relieve it with the guide wire, and on the lines described by Young and Maurer (1970).

If this fails then the knot is withdrawn to the bifurcation of the abdominal aorta, and an 8-French (Type I) catheter is then introduced into the opposite femoral artery, and passed through the knot and advanced into the more proximal aorta (Fig. 1B). The end of the knotted catheter is then manipulated using to-and-fro motions.

With the purchase obtained using this second catheter the knot is opened sufficiently to free the tip (Fig. 1C).

A small injection of contrast should be given prior to manipulation in order to assess the lumen size of the distal aorta and the presence of atheromatous plaques, as this may influence the amount of manipulation to be attempted.

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YOUNG, D. A., and MAURER, R. M., 1970. Manipulation of a knotted intravascular catheter allowing non-surgical removal. *Radiology*, *94*, 155–156.

Book review

Surgical Pathology of the Nervous System and its Coverings. By Peter C. Burger and F. Stephen Vogel, pp. xi + 623, illus., 1976 (John Wiley & Sons Ltd, Chichester, Sussex), £28·00.

As neuroradiology increases in sophistication it has become possible to show the structure and patho-physiology of the central nervous system and its coverings in progressively more detail. Computed tomography reveals the anatomy and physical composition of lesions in a manner similar to neuropathological sections so that distinctions between conditions which were previously beyond the scope of radiology, are now within its field. It is, therefore, of even greater importance than formerly for the radiologist to have considerable knowledge of the variations in morbid anatomy and histology which may occur in pathological processes.

This book presents neuropathology in a regional manner. The text is relatively short and not comprehensive but it emphasizes important features and it is supplemented by well selected up-to-date references to the literature. It certainly gives adequate detail for students of neuroradiology. There is a good index to the text and to the excellent illustrations which make the book suitable for use as an atlas.

It is recommended as a good introduction to the subject and as a useful source of references for those seeking more detailed knowledge.

B. KENDALL.

1977, *British Journal of Radiology*, *50*, 213–215

Case reports

Sclerosing haemangioma of the lung

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Vascular tumours of the lung are classified according to their cell of origin as haemangiopericytomas, haemangioendotheliomas, or sclerosing haemangiomas (Feldman and Seaman, 1964; Mori, 1968; Tralka and Katz, 1963). Of these three types, sclerosing haemangioma is the most common (Feldman and Seaman, 1964; Mori, 1968; Tralka and Katz, 1963), yet only 18 have been well documented in the English literature (Arean and Wheat, 1962; Edwards and Taylor, 1938; Goorwitch and Madoff, 1955; Haas *et al.*, 1972; Hill and Eggleston, 1972; Liebow and Hubbell, 1956; Magri *et al.*, 1957; Mori, 1968; Rubin *et al.*, 1958; Solomon and Wessely, 1959; Turunen *et al.*, 1957). We are reporting an additional case of pulmonary sclerosing haemangioma, to our knowledge the first in the radiologic literature.

CASE REPORT

An asymptomatic, 40-year-old woman had a routine chest X ray film in March 1975, and a solitary, right lung mass was detected. Sputum culture and cytologic findings were negative. Results of needle biopsy of the mass suggested alveolar cell carcinoma but were not diagnostic. In April 1975, the patient was admitted to our institution for thoracotomy. She had no history of cough, haemoptysis, dyspnoea, or recurrent respiratory infections. Physical examination was unremarkable. Haematocrit was 35%; white blood cell count was 5,900 mm^3 with a normal differential.

Chest X ray films demonstrated a well-defined, oval, somewhat lobulated, 2-cm mass in the right lower lobe (Fig. 1). On the tomogram, the mass appeared homogeneous, without evidence of cavitation or calcification; no other lesions were seen (Fig. 2).

Lobectomy of the right lower lobe was performed without complication. A firm, 2-cm nodule was disclosed below the right hilum; it did not extend to the visceral pleura. No abnormal lymph nodes were identified. On cut section, the mass was well circumscribed with a variegated surface, white to brown in colour.

The pathological diagnosis was sclerosing haemangioma. Microscopic examination demonstrated a circumscribed but nonencapsulated mass with a predominantly papillary configuration. The papillae were made up of numerous capillaries and blood-filled sinusoids and were covered with cuboidal cells having the appearance of alveolar epithelium (Fig. 3). A fibrous tissue stroma was present with areas of hyalinization. There were many areas of haemorrhage with large collections of foamy histiocytes; cholesterol clefts were scattered throughout the tumour. Calcification was found as well as a few chronic inflammatory cells. Adjacent bronchi were normal.

The patient is now well, with no evidence of recurrence of the tumour three months after surgery.

DISCUSSION

Sclerosing haemangioma of the lung was originally described by Liebow and Hubbell in 1956. It is a benign, vascular tumour and metastasis or recurrence following excision has not been reported (Mori, 1968). Sclerosing haemagioma is characterized histologically by (a) proliferation and sclerosis of vessels, (b) papillary projections of vascular tissue filling terminal air spaces, (c) areas of haemorrhage, and (d) infiltration of fibrous supporting tissues by fat and haemosiderin-laden histiocytes (Liebow and Hubbell, 1956; Mori, 1968). Microscopic calcification may occur within the tumour,

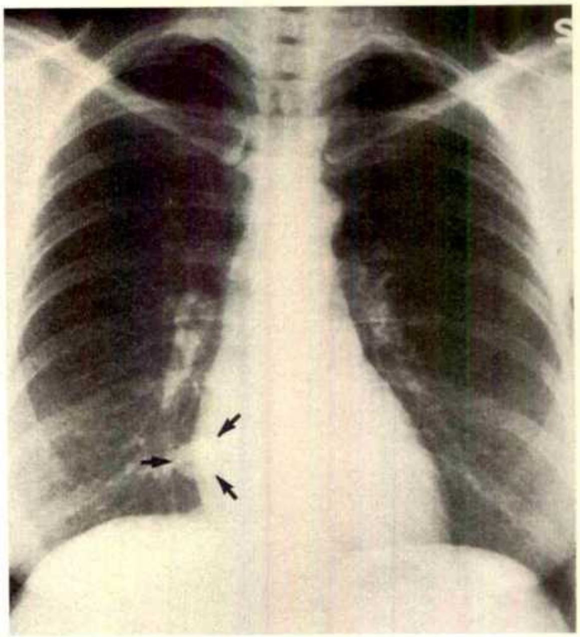

FIG. 1.

A.P. chest radiograph. A solitary well defined 2-cm nodule (arrows) is present in the right lower lobe.

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and cavitation has been reported pathologically (Liebow and Hubbell, 1956; Rubin *et al.*, 1958). As in our case, masses are usually well marginated by pseudocapsules of compressed lung parenchyma (Arean and Wheat, 1962; Liebow and Hubbell, 1956).

Because of the histologic similarities, a relationship between sclerosing haemangioma and pulmonary xanthoma or pulmonary histiocytoma has been suggested (Arean and Wheat, 1962; Hill and Eggleston, 1972; Liebow and Hubbell, 1956; Mori, 1968; Wentworth *et al.*, 1968). However, a recent ultrastructural analysis using the electron microscope has clearly differentiated sclerosing haemangioma from xanthomatous or histiocytic tumours (Haas *et al.*, 1972). A similar analysis has confirmed the vascular origin of this lesion (Hill and Eggleston, 1972).

Our case is typical of sclerosing haemangioma. Fourteen of the 18 reported cases have occurred in women, and 14 patients were between 30 and 60 years of age at the time of diagnosis (Arean and Wheat, 1962; Edwards and Taylor, 1938; Goorwitch and Madoff, 1955; Solomon and Wessely, 1959; Turunen *et al.*, 1957). Tumours were located in the right lower lobe in nearly half of the patients (Goorwitch and Madoff, 1955; Haas *et al.*, 1972; Liebow and Hubbell, 1956; Rubin *et al.*, 1958). In 17 patients the mass was solitary, but one patient had separate tumours involving left upper and left lower lobes (Turunen *et al.*, 1957).

Radiographic findings were reported in 15 of the cases we reviewed (Arean and Wheat, 1962;

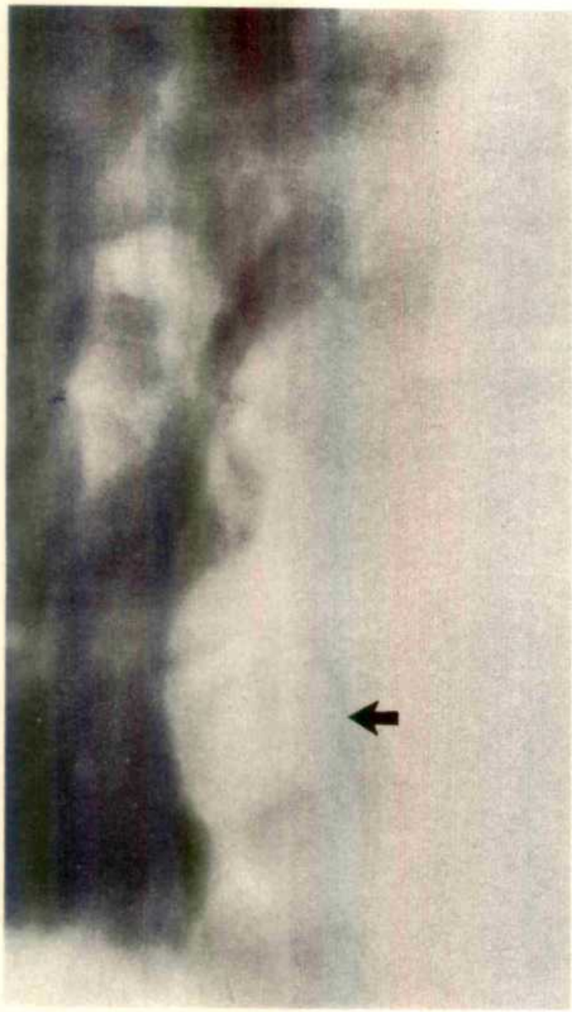

Fig. 2.

A.P. tomogram of the right lower lobe. The nobule (arrow) is homogeneous in density with a slightly lobulated contour.

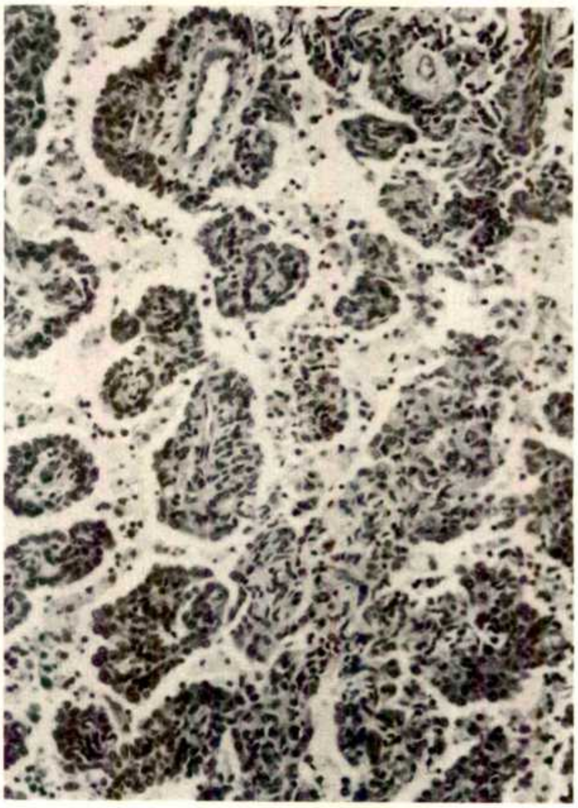

Fig. 3.

Photomicrograph (× 140). Epithelium-covered papillae contain large blood vessels. Some show hyalinization.

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Edwards and Taylor, 1938; Goorwitch and Madoff, 1955; Hill and Eggleston, 1972; Magri *et al.*, 1957; Rubin *et al.*, 1958; Solomon and Wessely, 1959; Turunen *et al.*, 1957). Sclerosing haemangioma frequently appeared as a round or oval density; lobulation has been noted (Edwards and Taylor, 1938; Liebow and Hubbell, 1956; Solomon and Wessely, 1959). Calcification or cavitation was not evident. The nodules ranged from 1.9 to 9 cm in diameter. Some grew slowly; in one case, however, no growth occurred during a 12-year period of observation (Liebow and Hubbell, 1956). Arteriography in two reported cases (Liebow and Hubbell, 1956; Solomon and Wessely, 1959) failed to demonstrate a communication between the tumour and pulmonary or bronchial circulations, and masses did not opacify with contrast material. At fluoroscopy, sclerosing haemangiomas did not pulsate and did not diminish in size during Valsalva's manoeuver (Mori, 1968; Rubin *et al.*, 1958).

Bronchography has demonstrated displacement of bronchi adjacent to the tumour, but bronchial occlusion or endobronchial invasion has not been seen in patients with this lesion (Arean and Wheat, 1962; Magri *et al.*, 1957). These findings have also been seen bronchoscopically and pathologically (Goorwitch and Madoff, 1955; Liebow and Hubbell, 1956; Mori, 1968; Rubin *et al.*, 1958; Solomon and Wessely, 1959; Turunen *et al.*, 1957).

Haemoptysis did not occur with our patient although it was the most frequent complaint of patients with sclerosing haemangioma (eight of the 18 reported cases) (Goorwitch and Madoff, 1955; Liebow and Hubbell, 1956; Magri *et al.*, 1957; Mori, 1968; Rubin *et al.*, 1958; Solomon and Wessely, 1959; Turunen *et al.*, 1957); indeed, one patient expectorated 500 ml of blood within 24 hours. Because sclerosing haemangioma does not involve the bronchus (Arean and Wheat, 1962), the frequency of haemoptysis in patients with this lesion probably is a reflection of its vascularity. Haemoptysis is uncommon with pulmonary tumours that do not involve the bronchial wall and so the association of a solitary, well defined nodule with haemoptysis and normal bronchographic or bronchoscopic findings should suggest sclerosing haemangioma.

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Plexiform mediastinal neurofibromas. A report of two cases

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(*Received August, 1976*)

We wish to report the chest X ray findings in two young children with neurofibromatosis, who showed unusual lobulated mediastinal widening.

CASE REPORTS

Case 1

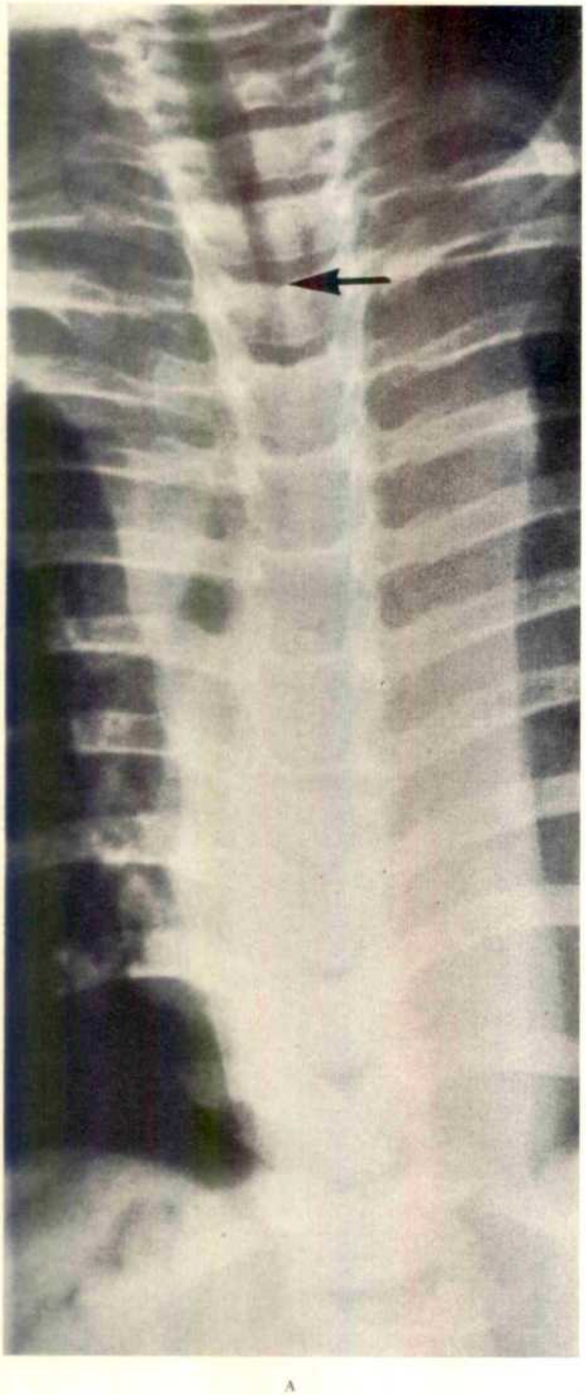
D.S., a two-year-old Jamaican negro boy presented with recurrent chest infections. Examination revealed soft masses in the left supra-clavicular region. *Café-au-lait* spots on the trunk were recognized at a later date. There was no family history of neurofibromatosis.

Chest radiography showed lobulated masses in the middle mediastinum extending from the lung apices to the diaphragm (Fig. 1). The trachea and left main bronchus were narrowed. Films of the cervical spine showed hypoplasia and backward subluxation of C.2. Three weeks after admission he developed stridor. Biopsy of the left supraclavicular mass revealed neurofibroma tissue. One month later thoracotomy was performed because of increasingly severe stridor. At operation a plexiform neurofibroma was found encircling the trachea, and this was freed. The patient developed asystole and died whilst a naso-gastric tube was being passed to relieve gastric distension in the post-operative period.

Autopsy demonstrated plexiform neurofibromatous masses throughout the mediastinum extending to surround the abdominal aorta. In the neck the neurofibroma extended through the intervertebral foramina to lie alongside the cervical cord and the medulla oblongata.

Case 2

P.M., a mentally-retarded boy of ten months, presented with cyanotic choking attacks, following a 24-hour febrille illness. He had *café-au-lait* spots on the trunk and thighs,



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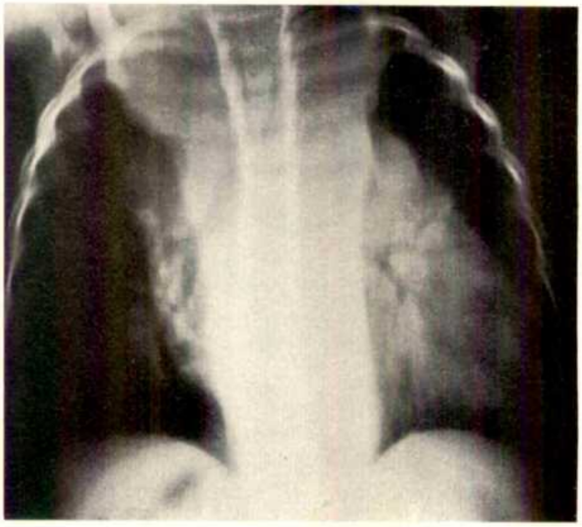

B

FIG. 1. *Case 1.*

A.P. chest film and tomography showing bilateral lobulated mediastinal widening extending the whole length of the chest, maximal in the superior mediastinum. The trachea is narrowed at the thoracic inlet (arrow 1A).

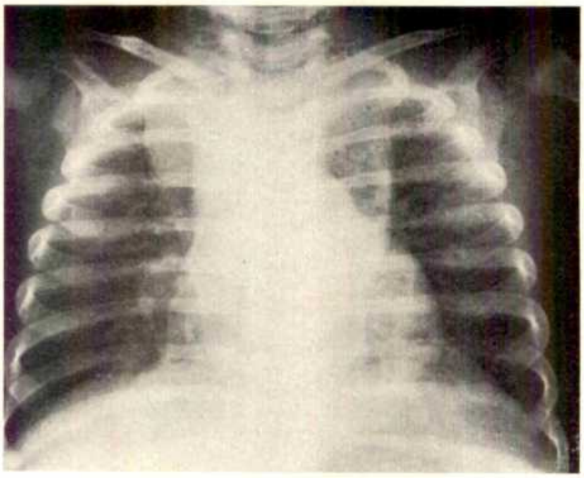

FIG. 2. *Case 2.*

A.P. chest film showing bilateral mediastinal widening, which, as in Case 1, extends the whole length of the chest and is maximal in the superior mediastinum.

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and the left leg was larger than the right. The mother had severe neurofibromatosis.

The chest radiograph showed bilateral lobulated widening of the posterior mediastinum (Fig. 2). The lungs were normal.

Following recovery from the acute illness, presumed to be a virus infection, he was discharged from hospital. Histology of the mediastinal masses was not obtained since the symptoms, signs and family history were considered sufficient for the diagnosis of neurofibromatosis. He has been followed for four years as an out-patient and there has been no change in the relative size of the posterior mediastinal widening.

DISCUSSION

Radiologically recognizable plexiform neurofibromas are rare. They may cause a diagnostic problem, particularly if, as in our first case, there is no family history or obvious skin lesions. It was only after the diagnosis of neurofibromatosis had been suggested by the radiologist that the abnormally pigmented patches of skin in this negro child were recognized as *café-au-lait* spots. Initially neuroblastoma and tuberculosis were considered as possible diagnoses. Even after the diagnosis of neurofibromatosis had been made, we were concerned that the masses in the chest film might be partly or wholly lateral meningocoeles since lateral meningocoeles are common in this condition (Klatte *et al.*, 1976). Raffensperger and Cohen (1972) reported a case somewhat similar to ours in a nine-year-old boy with neurofibromatosis who had bilateral neck masses and superior mediastinal extension.

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Congenital mesenchymal tumour of the lung

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Congential lung tumours are a rare cause of perinatal respiratory distress and death. Congenital adenomatoid malformation (Merenstein, 1969) and pulmonary hamartoma (Jones, 1949) have presented in this fashion. We have observed a newborn with anasarca, severe respiratory distress and radiographic evidence of a mass in the left hemithorax who died shortly after birth. The autopsy revealed a large mesenchymal tumour of the left lower lobe.

CASE REPORT

A 3500 gram full term baby girl, was born to a 24-year-old mother after an uncomplicated pregnancy of 40 weeks. The second stage of labour was slightly prolonged by shoulder dystocia.

The Apgar score was 0 at 1 min and endotracheal intubation was performed in the delivery room. The infant was cyanotic and responded poorly to stimuli. There was generalized pitting oedema, most marked over the abdomen. Rales were audible in both lungs and there was decreased aeration on the left. Peripheral pulses were poor. Cardiac sounds were audible on the right; there were no murmurs. The electrocardiogram was consistent with dextro position of the heart; voltage was decreased in all leads.

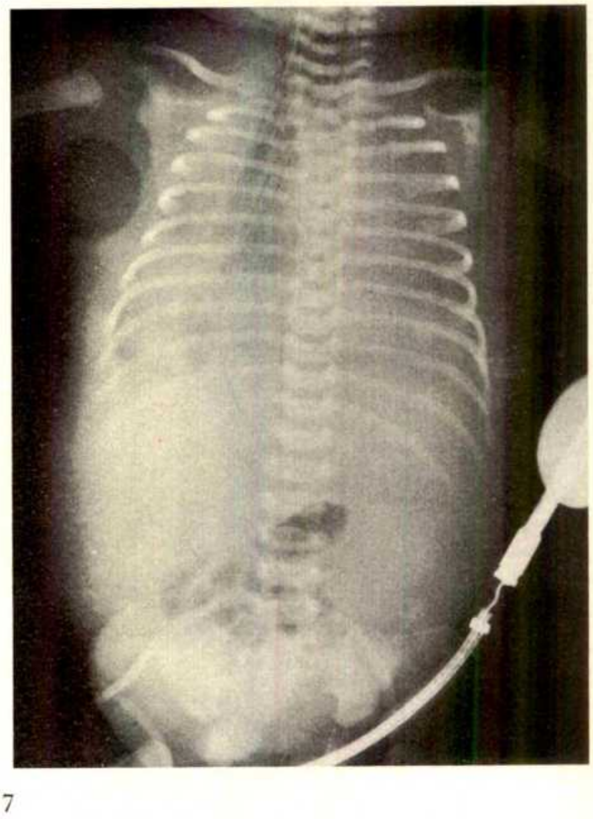


Fig. 1.

Radiograph of chest and abdomen. The infant's oesophagus (indicated by a nasogastric tube) and trachea are displaced far to the right. Aerated lung is visible at the right base. The stomach and proximal small bowel are displaced toward the midline by ascites. The body wall is oedematous.

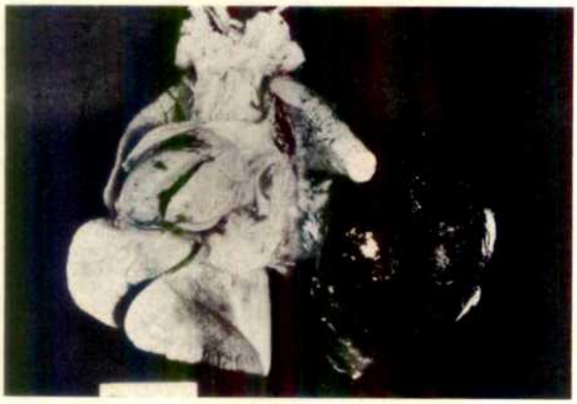


Fig. 2.

Heart and lungs, after fixation of the lungs *in situ* by perfusion with formalin at inflating pressure. Front view: A large tumour replaces the left lower lobe. The left upper lobe is atelectatic. The heart is dextroposed.

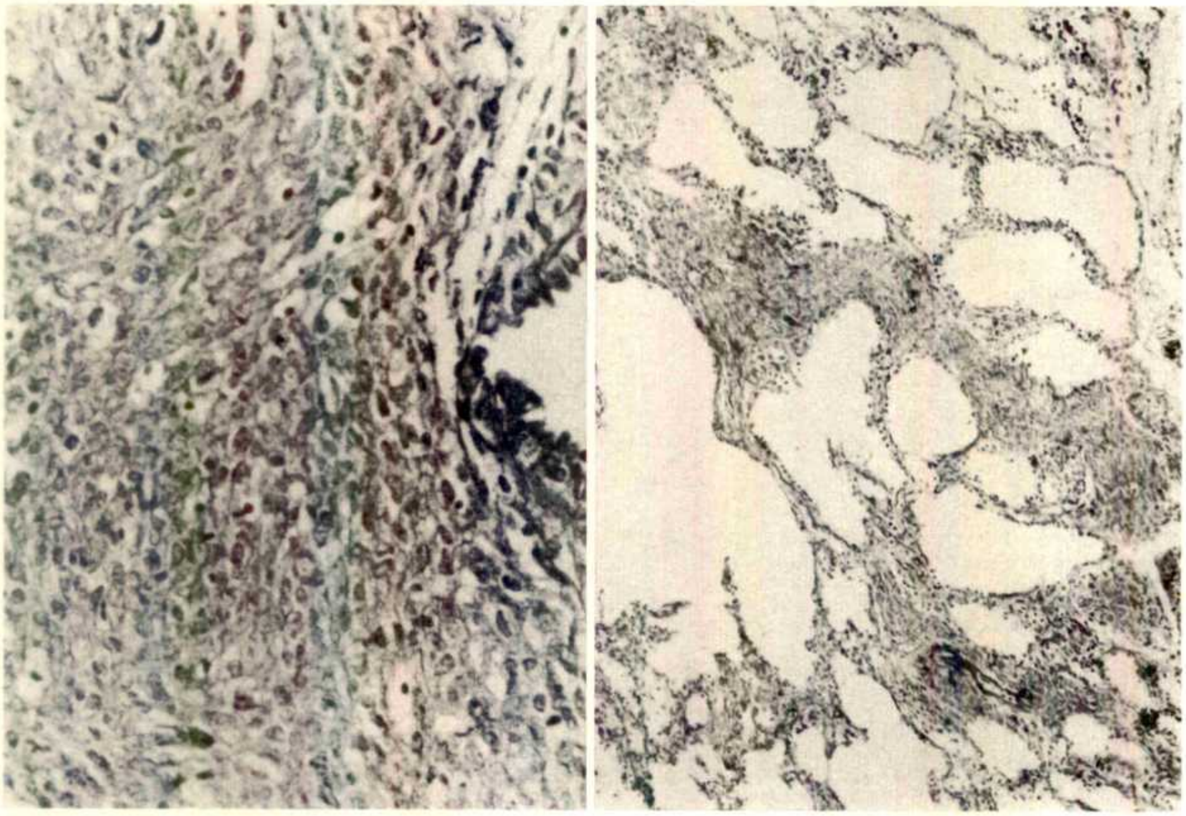
A radiograph of the chest obtained at two hours of age revealed opacification of the left hemithorax and a marked mediastinal shift toward the right. A small amount of aerated lung was visible at the right base (Fig. 1).

The infant's condition remained very poor. She made a few spontaneous respiratory efforts while receiving assisted ventilation on the Bird respirator. Severe acidosis was partially corrected by infusions of sodium bicarbonate. Intravenous adrenalin and calcium gluconate were needed to maintain her heart rate above 100 beats/min. Her central venous pressure was slightly elevated (12–15 mm of water).

Her condition continued to deteriorate and she died at eight hours of age.

Autopsy findings

Other than ascites and generalized oedema, the only significant abnormalities were found in the chest. Small pleural effusions were present bilaterally. There was a preductal coarctation of the aorta; the narrowed segment measured 0.3 cm in circumference when opened. The ductus arteriosus was widely patent. The left lower lobe was almost totally replaced by a large dark red tumour, which measured 5.5 by 4.0 cm, and the heart was displaced to the right (Fig. 2).



A B

Fig. 3.

(A) Low power photomicrograph of tumour. The tumour appears to arise from multiple foci in the mesenchyme adjacent to distal bronchi.

(B) Higher power. The tumour consists of elongated smooth muscle cells which are often separated by delicate reticulum fibres (Hematoxylin and eosin stain).

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Microscopically, the lung tumour appeared to arise multicentrically from the mesenchyme surrounding peripheral bronchioles. Most regions of the tumour consisted of nests of smooth muscle cells arranged in parallel bundles which were partially separated by delicate reticulin fibres (Fig. 3). Often the mesenchymal cells were indistinguishable from or continuous with the mesenchyme of adjacent alveolar walls. Trichrome stains for collagen were negative. The main tumour mass, which was grossly haemorrhagic, showed considerably less differentiation toward smooth muscle. Mesenchymal cells in the main tumour mass were rounded and had vaculoated cytoplasm, and were embedded in a myxomatous stroma. In more vascular areas tumour cells were present outside the reticulum sheaths of capillaries. No mitotic figures were found in any of the sections examined. Prominent foci of extramedullary haematopoesis were found throughout the tumour, especially in the most vascular areas. There was no invasion of blood vessels or bronchi, and there were no extrapulmonary extensions or metastases.

The final pathologic diagnosis was congenital mesenchymal tumour of the lung with leiomyomatous elements.

DISCUSSION

Benign pulmonary smooth muscle tumours are rare. Hirose and Hennigar (1955) reviewed 23 cases of pulmonary leiomyoma that had been reported up to 1954; three had occurred in children 4–8 years of age and one in a stillborn infant. These tumours are presumed to arise from mesenchyme associated with the bronchi and often present as intrabronchial masses (Watson and Anylan, 1951; Hirose and Hennigar, 1955). Pulmonary hamartomas containing epithelial and cartilaginous elements (bronchial rudiments) are more common than leiomyomas but are seldom symptomatic (Caffey, 1972).

Our patient's tumour appeared to arise multicentrically in mesenchyme surrounding peripheral bronchioles. The predominant cell type resembled the primitive stem cell of embryonal connective cells (Collet and Des Biens, 1974); the most differentiated cells in the tumour were smooth muscle cells. This tumour is quite distinct from mesenchymoma, which by definition comprises several types of differentiated tissue and is not known to occur in the lung (Mayer *et al.*, 1974; Nash and Stout, 1961).

Radiographically, our patient presented with an opaque haemithorax and a contralateral mediastinal shift. The differential diagnosis of this radiographic appearance in the newborn infant includes congenital diaphragmatic hernia, pleural effusion, chylothorax, haemothorax, lobar emphysema with fluid retention, neurenteric cyst, sequestration, bronchopulmonary foregut malformation and lung tumours such as congenital adenomatoid malformation (Caffey, 1972). To our knowledge, this is the first example of a congenital mesenchymal tumour of the lung that has presented in this fashion. Anasarca and ascites, striking features in our patient, have frequently been observed in stillborn and liveborn infants with congenital adenomatoid malformations. (Merenstein, 1969). Massive fluid retention in infants with congenital lung tumours is probably due to compression of the great veins by the large mass (Craig *et al.*, 1956). Our patient also had a serious cardiac defect (preductal coarctation of the aorta) which may have contributed to her severe perinatal distress.

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Congenital arteriovenous malformation of the pancreas

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(Received June, 1976)

Congenital arteriovenous malformations were first described by Busche in 1827 and Hewett in 1867 (Busche, 1827; Cross *et al.*, 1958). Callander and Pemberton's later work showed that congenital arteriovenous malformations were more common than had previously been thought by Callander (Pemberton and Saint, 1928; Callander, 1920).

It was previously thought that congenital arteriovenous malformation involved only extremities, but more recently there have been reports of involvement of the bowel (Baum, 1971), brain and spinal cord (Newton and Troost, 1974), kidney (Gold *et al.*, 1965), liver (Martin *et al.*, 1965), uterus (Bottomley and Whitehouse, 1975), stomach (Pastershank *et al.*, 1974), mesentery (Anderson *et al.*, 1972), spleen (Tada *et al.*, 1969), heart (Currarino *et al.*, 1959), and lungs (Good, 1961). An arteriovenous fistula of the head of the pancreas was described in 1973 (Grannis *et al.*, 1973). It seems probable that this fistula was the result of ulcer disease and not a congenital malformation. The purpose of this report is to describe a case of congenital arteriovenous malformation of the entire pancreas and to review briefly current methods of diagnosis and treatment of these congenital lesions.

CASE REPORT

A 35-year-old woman presented with an eight-year history of mid-epigastric pain radiating through to the back and relieved by leaning forward; there was associated nausea and vomiting. She had experienced monthly episodes of this pain from 1968 to 1971, but there were no further problems until five weeks prior to her current hospital admission in 1975, when her symptoms suddenly returned. During this five-week interval, there was a nine kilogramme weight loss, several hospital admissions were required, and the symptoms progressed until large doses of narcotics were necessary to control the pain. Serum amylases were 92 and 81. Upper gastrointestinal series was normal.

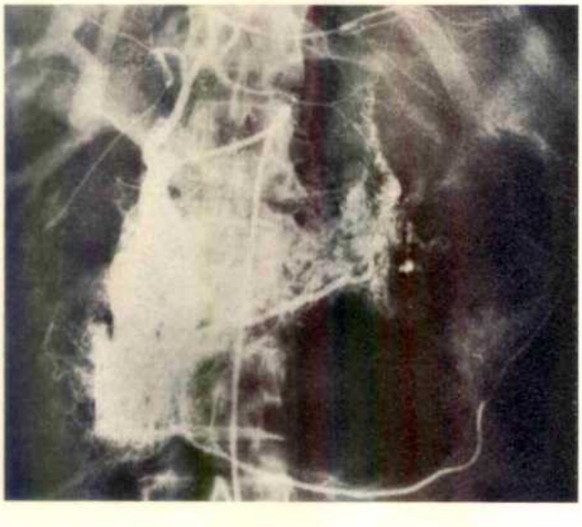

FIG. 1.

Selective gastroduodenal injection showing arteriovenous malformation in the pancreas. The stomach and duodenum are filled with air, showing the extent of the malformation. The portal vein shows early filling because of shunting of blood through the malformation.

Angiography showed a large arteriovenous malformation involving the entire pancreas (Figs. 1, 2 and 3). The gastroduodenal and superior mesenteric arteries were the major arterial supply for the malformation. There were two smaller arteriovenous malformations in the jejunum. The patient's epigastric pain radiating to the back occurred with each injection of the pancreatic arteriogram.

Conservative therapy was chosen since surgery could offer only a Whipple procedure, which would be of questionable merit. Xylocaine coeliac plexus block was successful in eliminating the patient's pain. A subsequent ethanol neurolytic block was performed.

DISCUSSION

The findings in the patient described herein are quite unlike the case of hypervascularity and arteriovenous shunting in a biopsy-proven case of pancreatitis reported by Roe and Greenough (1974). The vascular lesion is larger, and there are similar lesions in at least two locations in the small bowel (Fig. 3).

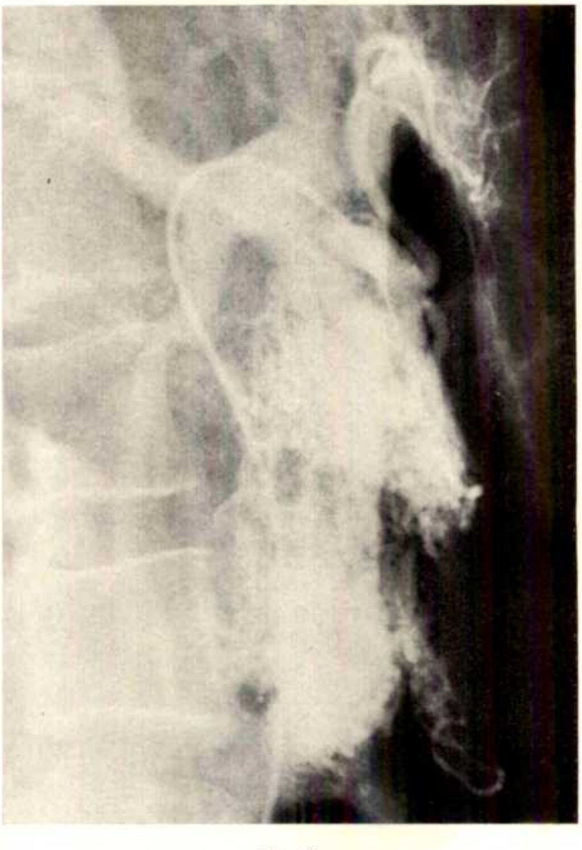

FIG. 2.

Lateral view of gastroduodenal injection shows the pancreatic malformation.

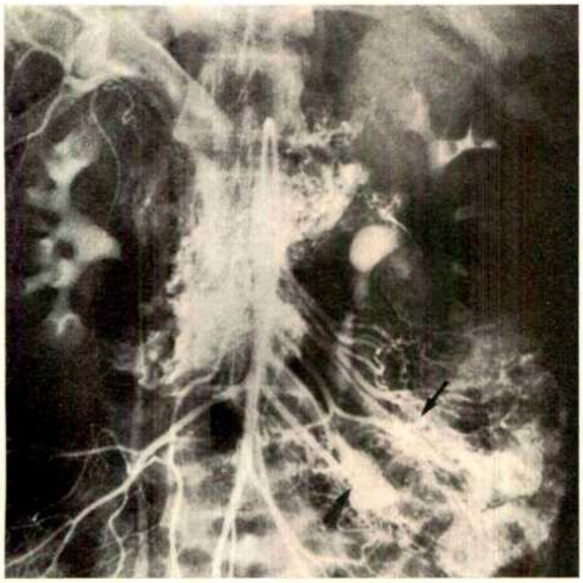

FIG. 3.

Selective superior mesenteric injection showing the superior mesenteric artery's contribution to the arteriovenous malformation. Note the two additional malformations (arrows) in the small bowel.

The treatment of arteriovenous malformations has long been a problem. Complete excision offers the best chance for cure, and wherever possible this is the treatment of choice. Where complete excision is not possible or indicated, alternative forms of surgery are available (Holman, 1968; Malan and Puglionisi, 1965; Perret and Nishioka, 1966).

In spite of advances in diagnosis and surgical technique, there remain cases of congenital arteriovenous malformations that are not treatable by any type of surgery. Other forms of treatment have been attempted, including bed rest and anticonvulsant therapy in cases of intracranial arteriovenous malformations (Perret and Nishioka, 1966), and the use of elastic bandages to reduce some of the signs and symptoms of extremity arteriovenous malformations (Malan and Puglionisi, 1965). Röntgen therapy and radium have been attempted, but they have had little beneficial effect (Malan and Puglionisi, 1965). Sclerosing solutions have been used to treat extremity arteriovenous malformations (Malan and Puglionisi, 1965; Smith and Horton, 1937).

Intraoperative embolization of intracranial arteriovenous malformation with muscle was first reported by Hamby and Gardner (1933), and various reports of embolization techniques have appeared since then (Gurdjian, 1938; Luessenhop *et al.*, 1962; Luessenhop and Spence, 1960). The technique of embolization of intracranial arteriovenous malformations can be safe in "selected patients" when biplane angiography is used to predict and plan the path of the embolus (Luessenhop *et al.*, 1965). Intra-arterial embolization has been used in conjunction with surgery to make the surgery easier and safer, and in unresectable arteriovenous malformations as the primary therapy (Olcott *et al.*, 1976).

Although embolization has been used with favourable results in the treatment of certain intracranial congenital arteriovenous malformations, in some mandibular and maxillary arteriovenous malformations prior to indicated dental extractions (Hoey *et al.*, 1970) and in post-biopsy fistulae in the kidney (Bookstein and Goldstein, 1973; Risk *et al.*, 1973), this procedure was not attempted in the case reported herein. The inaccessibility of the lesion and the likelihood of infarction of portions of the small bowel made the procedure unattractive.

Recently another procedure for the treatment of congenital arteriovenous malformations has been tried. This method employs radio-frequency thrombosis of the malformations using a magnetic electrode catheter guided to the arteriovenous malformation with fluoroscopic control. Radio-frequency heating of the catheter tip leads to occlusion of the abnormal vessels (Gardner and Stewart, 1972; Taren and Gabrielsen, 1970). The outcome of these forms of therapy remains to be evaluated.

No matter what the form of therapy, arteriography is indispensable in the treatment of these lesions (Olcott *et al.*, 1976; Steinberg *et al.*, 1963).

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Interstitial gastric emphysema in a child with duodenal stenosis

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Gastric emphysema is due to gas in the stomach wall. This is an extremely rare condition, but may be recognizable radiologically. In the case recorded here, gastric emphysema was detected by plain film radiography in a child with a duodenal septum.

CASE REPORT

A nine month old child with Downs' syndrome was admitted on 9.4.76, with an attack of projectile vomiting. The child had had similar attacks since the age of seven months. Each attack lasted several hours and settled down without any active treatment. In between each attack, which occurred at about four weekly intervals, the child was sympton free. The presenting attack started on 5.4.76, and gradually became worse in the frequency and intensity of vomiting. No other symptoms were present and the child was quiet in between the bouts of vomiting. On examination, there was no evidence of dehydration. There was distension of the epigastrium with visible peristalsis. The temperature was not raised and the blood count was normal. There was no evidence of bile in the vomitus.

Radiological findings

On admission, erect and supine films of the abdomen were taken (Figs. 1 and 2). There was distension of the stomach, with an unusual translucent "halo" around the stomach. The erect film showed two air-fluid levels, one of which was in the fundus of the stomach. Normal intraluminal gas was present in the small bowel and also in the large bowel. There was no evidence of any free peritoneal air. A barium meal examination was undertaken following

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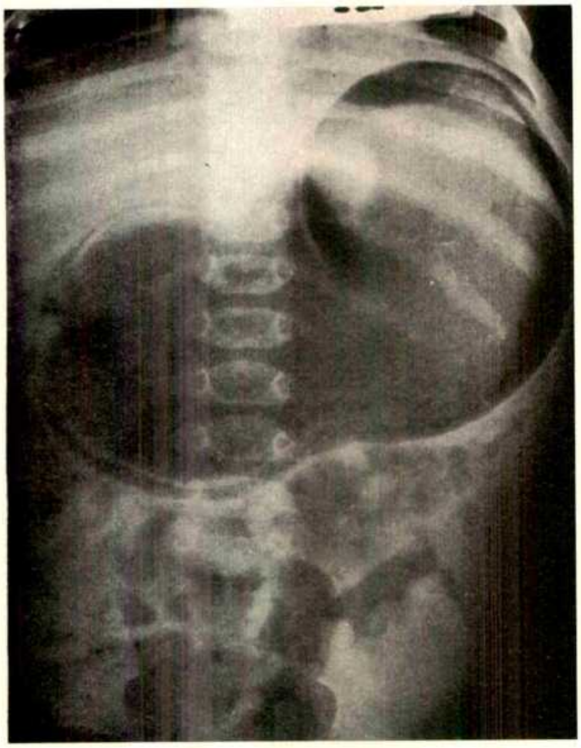

FIG. 1.

Gas filled stomach with an unusual translucent "halo" due to the presence of gas in the stomach wall.

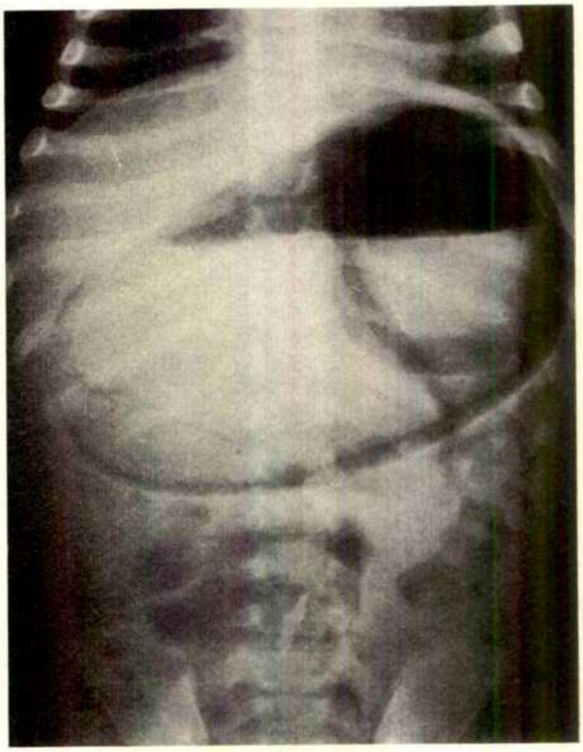

FIG. 2.

Air-fluid level in the fundus of the stomach and in the distended duodenum.

aspiration of the resting gastric juice. The barium (Fig. 3) outlined the distended stomach and confirmed the presence of gas in the stomach wall. The intramural gas was extensive, involving both the greater curvature and the lesser curvature. The intramural gas was restricted to the stomach wall and did not extend into the oesophageal or duodenal walls. The first part of the duodenum also appeared distended. A short markedly narrowed segment was outlined in the first part of the duodenum. The duodenum distal to this narrowing was of normal calibre and the small bowel also appeared normal.

Operative findings

The abdomen was opened by a transverse incision in the right hypochondrium. The stomach was large and the wall appeared thick with a feeling of crepitus. The proximal duodenum also appeared distended with a marked constriction distally. At this stage, the duodenum was opened at the site of the constriction, and a thick-walled muscular septum was visualized. There was a small opening in the centre of the septum. On division of the septum, the duodenal mucosa was seen to be partially intussuscepted into the distal part of the duodenum. Since the stomach felt thick and emphysematous, it was decided to open the stomach. A small incision was made in the mucosa and air forced itself out of the mucosal layer confirming the radiological finding. The stomach was closed in two layers. The septum was excised and the duodenoplasty was undertaken. The child had an uneventful recovery and post-operative follow-up films taken next day showed complete disappearance of the gastric emphysema.

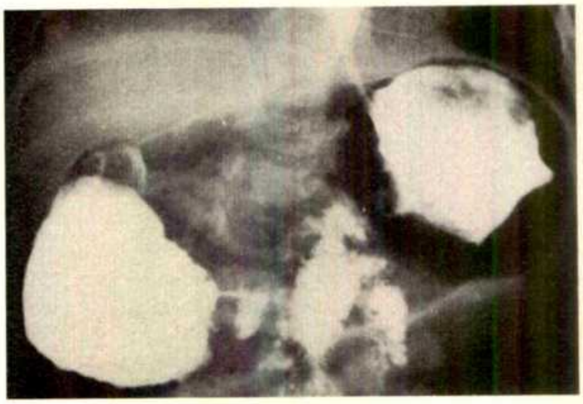

FIG. 3.

Barium in the stomach confirms the presence of extraluminal gas in the stomach wall.

CONCLUSION

This case is presented as interstitial gastric emphysema produced as a complication of duodenal obstruction. There was no evidence to suggest infection by gas-forming organisms or any history of instrumentation, and therefore the diagnosis of

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interstitial gastric emphysema, secondary to obstruction, is proposed.

DISCUSSION

The mechanism of production of gastric emphysema in this patient can be explained by a simple process. The stomach was chronically distended due to incomplete obstruction of the duodenum. There was sudden rise of intragastric pressure during the bouts of vomiting. At the height of raised intraluminal pressure, there was breach of the gastric mucosa and air escaped into the submucous layer. A similar process is described by Ward (1960) in an adult patient with pyloric stenosis due to gastric carcinoma. Fierst and his colleagues (1951) have postulated a similar mechanism in gastric emphysema following gastroscopy when the stomach is inflated and there is a rise in intragastric pressure.

Interstitial gastric emphysema may also be produced by other instrumentations as in sigmoidoscopy, oesophagoscopy, retroperitoneal air insufflation and therefore a history of instrumentation must always be sought. It is also described as a rare extension of pneumoperitoneum. Vichi and his colleagues (1973) have described 18 cases of necrotizing enterocolitis with intramural bowel gas, four cases of which showed gas in the stomach wall.

SUMMARY

A case of interstitial gastric emphysema secondary to duodenal obstruction is reported here. Localized involvement of the stomach wall is extremely unlikely in necrotizing entercolitis. In the absence of signs of infection, or a history of instrumentation or immuno-suppressive therapy, a lesion producing gastric or duodenal obstruction should be suspected. The presence of intramural gas should in no way alter the management. A barium examination will usually demonstrate the site of obstruction.

ACKNOWLEDGMENTS

I would like to thank Professor R. B. Zachary for permitting me to publish this case and also acknowledge the encouragement by Dr. R. K. Levick with his guidance and helpful suggestions.

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Reactivation of radiation pneumonitis by adriamycin

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The onset and severity of radiation pneumonitis depend on the total dosage, fractionation technique, the duration of treatment (Evans, 1960; Jennings and Arden, 1962) and concomitant chemotherapy (Littman *et al.*, 1974).

The ability of actinomycin D to potentiate and reactivate the effects of radiation in the skin (Liebner, 1962), mucosa (D'Angio *et al.*, 1959) and in the lungs is well known (Wara *et al.*, 1973) and a similar toxic effect has been ascribed recently to adriamycin (Donaldson *et al.*, 1974; Cassady *et al.*, 1975). We wish to report a case in which pneumonitis was activated by actinomycin D and reactivated by adriamycin, but in which empirical steroid therapy enabled the course of treatment to be continued. The important implications of these phenomena for current developments in treatment planning are discussed.

CASE REPORT

A female, aged four presented with a three week history of abdominal pain and haematuria. On examination there was a large mass in the left flank. Excretion urography showed delayed excretion of contrast medium in the lower part of the left kidney and an extensively disorganized pelvicalyceal system. A diagnosis of nephroblastoma was made. Chest radiograph showed multiple metastases (Fig. 1). Left nephrectomy was performed on 17/12/74. The diagnosis was confirmed histologically.

On the day of operation treatment was started with vincristine 0.75 mg/m^2 intravenously, and actinomycin D 0.015 mg/kg daily for five consecutive days. Vincristine 1.5 mg/m^2 was continued weekly for five weeks. On the 10th postoperative day abdominal irradiation was started but was interrupted after three days because the pulmonary metastases were enlarging. Therefore, on the 14th day irradiation of the whole of both lungs was begun and a dose of 1500 rad in 17 days in 10 fractions was given using opposed fields and ^{60}Co radiation. On the 21st day post-operatively adriamycin 35 mg (50 mg/m^2) was given. On the 30th day a chest radiograph showed complete radiological resolution of the metastases (Fig. 2).

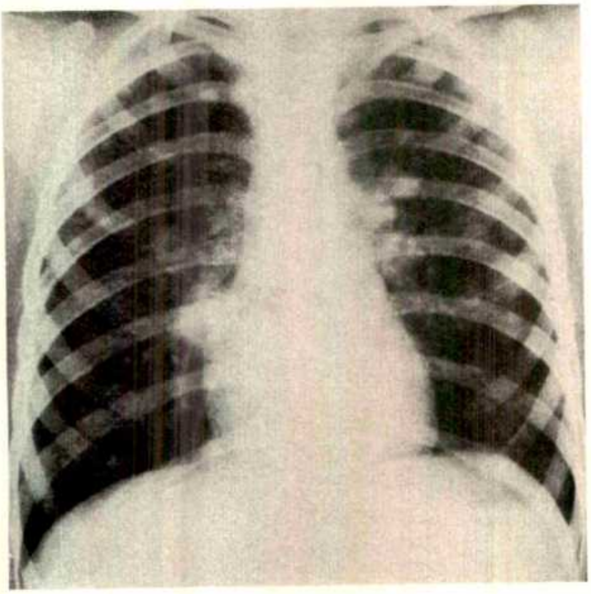

FIG. 1.

Multiple rounded opacities are seen throughout both lungs consistent with metastases.

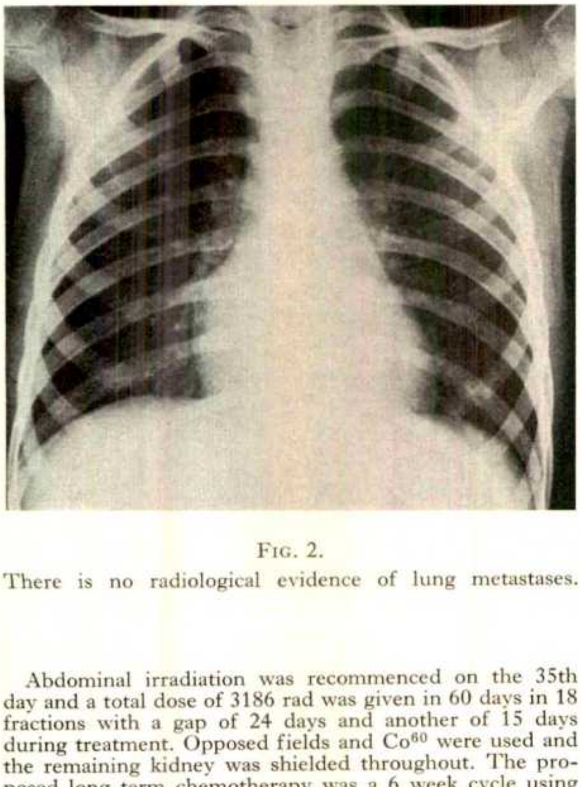

FIG. 2.

There is no radiological evidence of lung metastases.

Abdominal irradiation was recommenced on the 35th day and a total dose of 3186 rad was given in 60 days in 18 fractions with a gap of 24 days and another of 15 days during treatment. Opposed fields and Co^{60} were used and the remaining kidney was shielded throughout. The proposed long term chemotherapy was a 6 week cycle using actinomycin D 0.015 mg/kg on days 1 to 5 and adriamycin 50 mg/m^2 on day 22 with vincristine 1.5 mg/m^2 on days 1, 8 and 22.

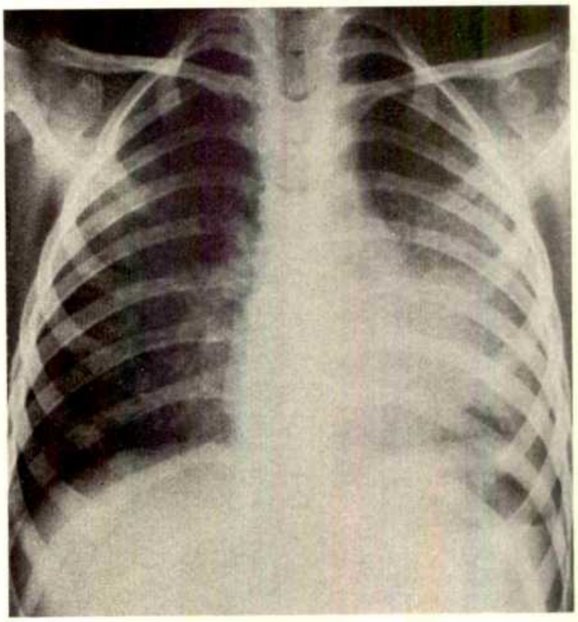

FIG. 3.

Opacification of the left mid and lower zone and interstitial thickening in the right mid zone are present due to radiation pneumonitis.

On the 100th day the third course of actinomycin D was finished. Four days later the patient developed acute otitis media which was treated successfully with antibiotics. On the 111th day the patient became acutely short of breath with central cyanosis. The pulse rate was 140/min., the respiratory rate 40/min. and the temperature normal. The chest radiograph showed a large opacity in the left lung, obscuring the heart border and patchy opacification in the right mid zone (Fig. 3). These were regarded as features of radiation pneumonitis and because of the clinical urgency treatment with prednisolone 15 mg. daily was started at once, without lung biopsy. Symptoms were relieved within 24 hours on this treatment and no pathogens were cultured from sputum or blood. The dose was tapered off over three weeks and then stopped. The chest radiograph (Fig. 4) showed almost complete clearing of the pneumonitis.

On the 133rd day the patient became acutely dyspnoeic, 24 hours after a planned dose of adriamycin. Prednisolone was restarted at 20 mg. daily with prompt relief of symptoms. The chest radiograph showed extensive opacification of the left lung (Fig. 5). The dose was gradually reduced over 3 weeks but when it was stopped cough and breathlessness rapidly returned and a maintenance dose of 5 mg. prednisolone daily was instituted. This dosage was continued in the form of enteric-coated capsules after a melaena on the 140th day. On the 190th day the chest radiograph showed a little diffuse opacification at the left base and left perihilar region (Fig. 6).

Subsequent doses of actinomycin D and adriamycin were given with steroid cover without adverse effect. Adriamycin was discontinued after a total dose of 200 mg/m^2 on the 200th postoperative day. A new régime of actinomycin D 1.4 mg/m^2 on day 1 and vincristine 1.5 mg/m^2 on days 1, 8 and 15 of a 6-week cycle was adopted. Enteric-coated prednisolone 2.5 mg. daily was given from days 1 to 22 of each cycle.

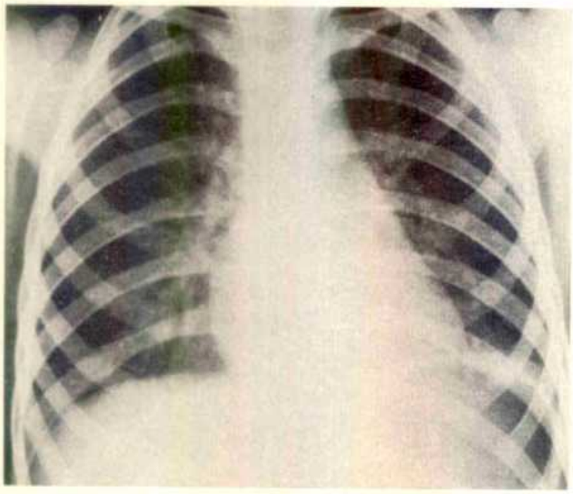

Fig. 4.
Almost complete clearing of the radiation pneumonitis has occurred.

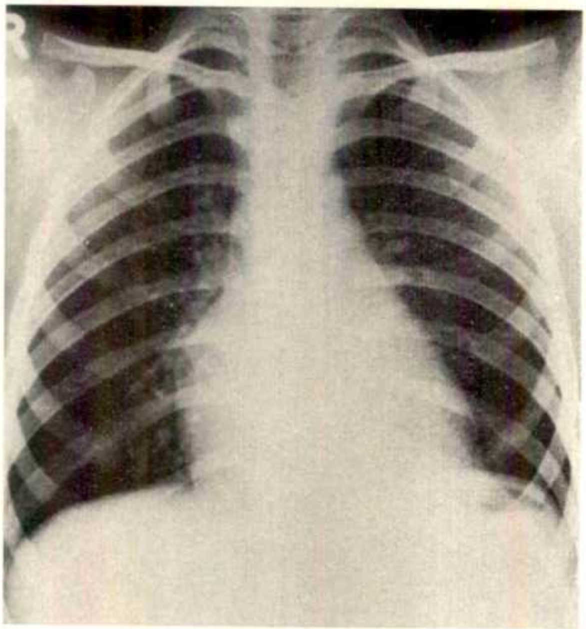

Fig. 6.
No lung lesion is shown on the final radiograph.

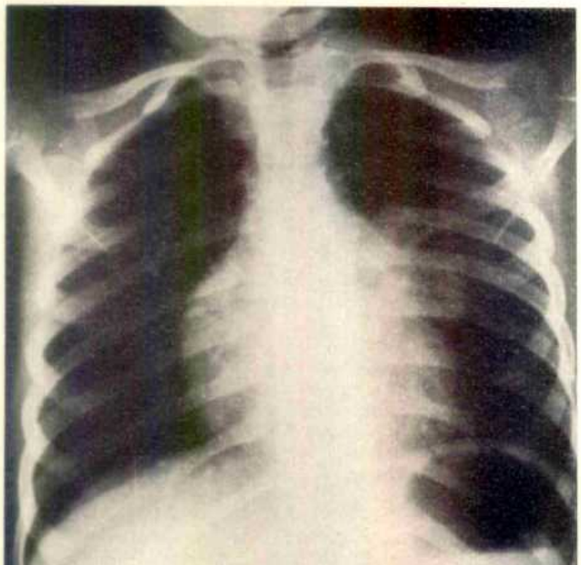

Fig. 5.
Patchy opacification of the left mid zone due to recurrent radiation pneumonitis.

The child remains well apart from a slight cough. She attends full-time school and takes part in games. Her chest is radiologically clear at follow-up to 15 months.

Discussion

Radiation pneumonitis occurs in 5 per cent of cases receiving a nominal standard dose (Ellis, 1968) of 900 rets, or of 700 rets with actinomycin D (Phillips and Margolis, 1972); and for a given dose of radiation, pneumonitis develops more frequently in those also given actinomycin D (Margolis and Phillips 1969). Usually there is an interval of two to three months between conventional radiation dosage and the onset of pneumonitis. In this case the total radiation dosage to the lungs of 656 rets was unlikely alone to cause pneumonitis. A dose of adriamycin 35 mg was given on the 7th day of lung irradiation and appears to have lowered the lung tolerance to a similar degree to that expected if actinomycin D were given concurrently with radiation. It is likely that the radiation effect was potentiated by the chemotherapy. Pneumonitis occurred 11 days after a dose of actinomycin D, three months after the start of lung irradiation. It was recalled 24 hours after subsequent treatment with adriamycin.

The empirical use of corticosteroids in treating radiation pneumonitis is supported by experimental studies in which their use increased the compliance of irradiated lungs in rats (Moss *et al.*, 1966); and it is reported that clinical and radiographic evidence of pneumonitis may occur within days of steroid withdrawal in patients with malignant lymphomas receiving radiotherapy to the chest and cyclic chemotherapy (Castellino *et al.*, 1973, 1974). Corticosteroid cover treatment may enable adriamycin and actinomycin D treatment to be completed despite the risk of reactivating radiation pneumonitis.

The combined disciplinary approach of surgery, radiation and chemotherapy in the treatment of malignant disease is being applied to an increasing number of tumours. When radiation and chemotherapy are used concurrently, modification of radiation dosage will be necessary if excessive normal tissue damage is to be avoided. When adriamycin is administered concurrently with radiation, pneumonitis may occur at an N.S.D. level below 700 rets. Corticosteroid cover allows treatment with adriamycin and actinomycin D to be continued despite recall radiation pneumonitis.

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The solitary ulcer syndrome of the rectum: radiological features

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The solitary ulcer syndrome of the rectum is a well defined pathological entity. The name was coined by Lloyd Davies at St. Mark's Hospital, London, during the 1930s. The condition was first described by Cruveilhier (1870) as a chronic ulcer of the rectum. Allen (1966) called it a hamartomatous polyp of the rectum and others have called it colitis cystica profunda (Epstein *et al.*, 1966; Wayte and Helwig, 1967). Madigan and Morson (1969) reviewed 68 cases that had been collected at St. Mark's Hospital and the subject has been recently reviewed by Rutter and Riddell (1975).

Despite its pathological and clinical recognition, however, the condition appears to be largely unknown to radiologists, with no reports in the radiological literature. The following case report shows, however, that it is of radiological significance.

CASE HISTORY

The patient, a 17-year-old girl, presented with a three year history of intermittent rectal bleeding which recently had become more frequent. She was otherwise fit. On clinical examination the only abnormality was a polypoidal mass in the rectum about 6 cm from the anal margin. Routine laboratory tests were normal. Sigmoidoscopy confirmed a mass at 6 cm involving two-thirds of the circumference of the rectal lumen. The mucosa above and below was normal. Biopsy of this area showed a large increase in fibrous tissue with abnormally sited deep glandular elements. A tentative diagnosis of an ulcerated granulomatous polyp was made. A barium enema showed non-distensible annular narrowing in the rectum (Fig. 1). An irregularity in the mucosa was thought to be due to the biopsy site. The barium enema was otherwise normal. Despite the young age of the patient, it was suggested that this lesion was probably malignant. Biopsy specimens taken at a sigmoidoscopy under G.A. showed similar histological appearances and because of the doubt raised by the deep glandular structure in the biopsy specimens, these were sent to Dr. Basil Morson at St. Mark's Hospital, London, for his opinion. Dr. Morson was in no doubt that the appearance was typical of

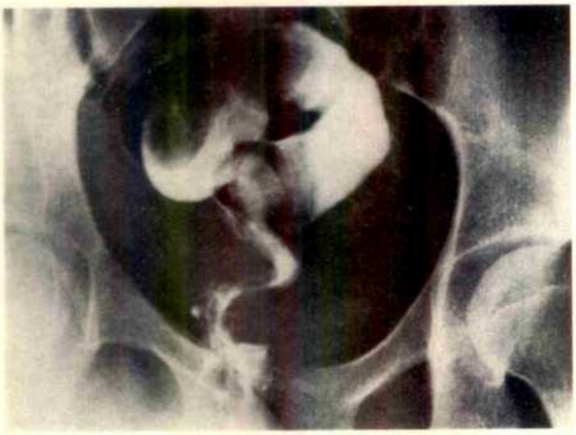

Fig. 1.

A non-distensible annular narrowing of the rectum shown by double contrast barium enema.

the solitary ulcer syndrome and reported: "Microscopically there is a rather characteristic obliteration of the lamina propria of the mucous membrane by collagen and smooth muscle fibres growing up from the excessively thickened muscularis mucosae. Reactive hyperplasia of the crypts was present, as is usual with ulceration, membrane formation and vascular dilatation."

Discussion

Solitary ulcer of the rectum syndrome occurs mainly in young people. The sex incidence is equal. The principal symptom is rectal bleeding. There is occasional passage of mucus. Pain is infrequent. The syndrome is thought to occur in those who strain at stool and it is suggested that failure of inhibition of the muscular sling formed by the puborectalis muscle lying posteriorly at the recto-anal junction, causes straining with prolapse of the rectal mucosa into the anal canal where it becomes traumatized (Rutter, 1975). Ulceration usually results but is not always present.

A history of straining at stool was not elicited in our case, but this is not a subject about which patients talk freely and many accept straining as normal. Rutter and Riddell (1975) state that the barium enema usually makes no contribution to the diagnosis, but may show unrelated colonic disease such as diverticular disorder. In the series of Madigan and Morson (1969), of their 68 patients, 35 had a barium enema. In 22 patients the enema was normal, eight had apparently unrelated conditions of the colon such as mild diverticular disease and five had a narrowing and irregularity of the rectal wall.

This irregular narrowing is probably similar to the lesion shown in our case. Ulceration is not shown, but need not be present for the diagnosis. Diagnosis depends on sigmoidoscopy and rectal biopsy with the pathological differential diagnoses of Crohn's disease, ulcerative colitis, villous adenoma and rectal carcinoma. We do not suggest that there are any specific radiological features to indicate the solitary ulcer syndrome and any rectal abnormality is presumably due to the fibrosis. The radiologist is, however, often the first link in the diagnostic chain and the finding of rectal narrowing in a young patient with rectal bleeding should suggest the solitary ulcer syndrome as a diagnosis, especially as an alternative to malignancy.

Acknowledgments

We are indebted to Dr. Basil Morson for making the diagnosis. We would also like to thank Mr. J. Magell for the sigmoidoscopy and biopsy and Mr. R. Graham for the photography.

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MARCH 1977

Case reports

Arteriographic diagnosis of appendiceal abscess

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(*Received August, 1976*)

Left upper quadrant appendicitis is an unusual and often puzzling diagnostic problem. Approximately 200 cases of left-sided appendicitis have been reported in the literature, and of these only four have been in the left upper quadrant (Smith *et al.*, 1974). When the diagnoses were made preoperatively they were made on the basis of a barium enema examination that showed non-rotation of the colon with the caecum lying in the left upper quadrant.

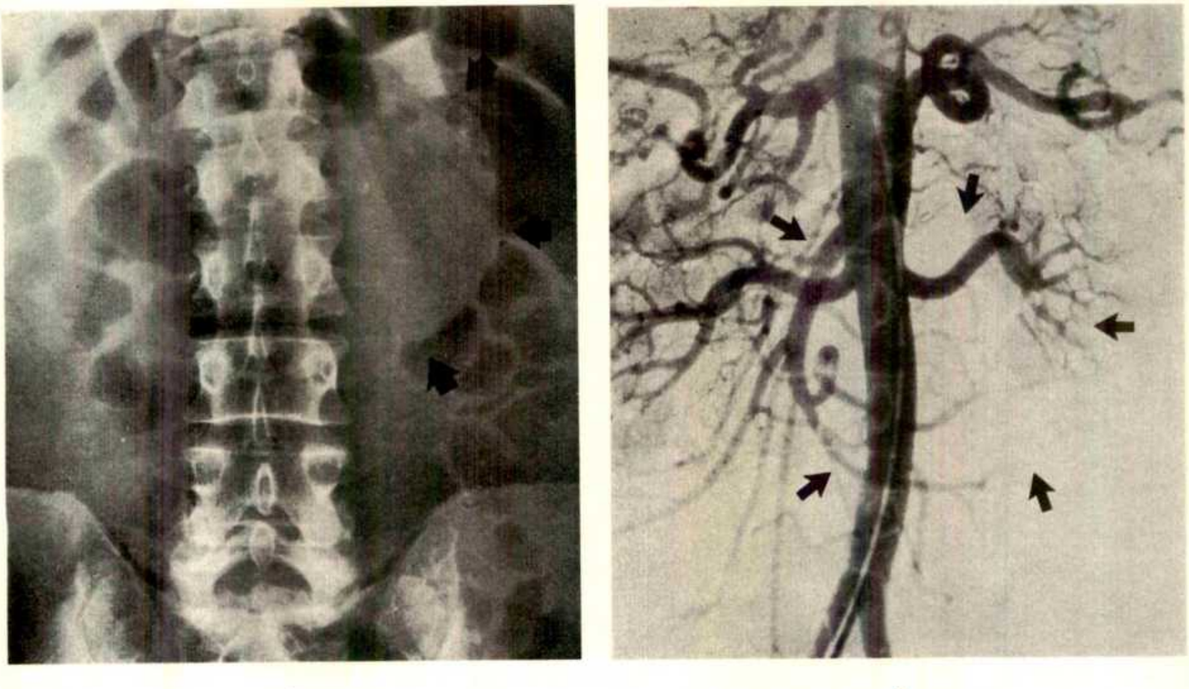
Recently, we were able to make the diagnosis preoperatively using angiography alone. Accurate identification of the arterial anatomy made this possible. This report emphasizes the value of such careful attention to vascular detail.

CASE REPORT

A 53-year-old man went to his physician after three weeks of dull constant pain in the left upper quadrant of his abdomen. He recalled some fever and chills. His physician palpated a pulsatile mass in the left upper quadrant and admitted the patient to our hospital for angiography and surgery of a suspected abdominal aneurysm. On admission his blood pressure was 115/75 mmHg and his temperature was 38.2°C. A white blood cell count of 16,700 was the only abnormal laboratory value.

The preliminary film for the arteriographic examination showed a non-calcified, soft tissue mass in the left upper quadrant (Fig.1A). Injection of contrast material demonstrated displacement of the superior mesenteric artery around this mass, which was avascular (Fig.1B). Further analysis of the anatomy of the branches of the superior mesenteric artery revealed that the ileocolic artery and the ileocolic loop were present in the left upper quadrant in the region of the mass (Fig.2A). Injection of the coeliac artery with contrast medium demonstrated a hypervascular stain around the mass with blood supply from omental vessels (Fig. 2B). The diagnosis of intra-abdominal abscess involving the omentum, possibly from a ruptured appendix, was made.

At operation, the caecum was seen in the left upper quadrant, and there was evidence of a ruptured appendix with a peri-appendiceal abscess sealed in by a covering of omentum.



A B

FIG. 1.

(A) Plain abdominal film shows soft tissue mass (outlined by arrows).

(B) Mass (arrows) is seen to be avascular with arcing of the superior mesenteric artery around it (subtraction film).

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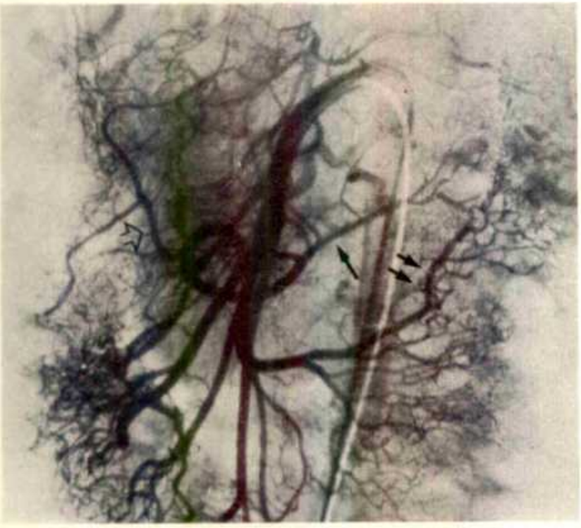

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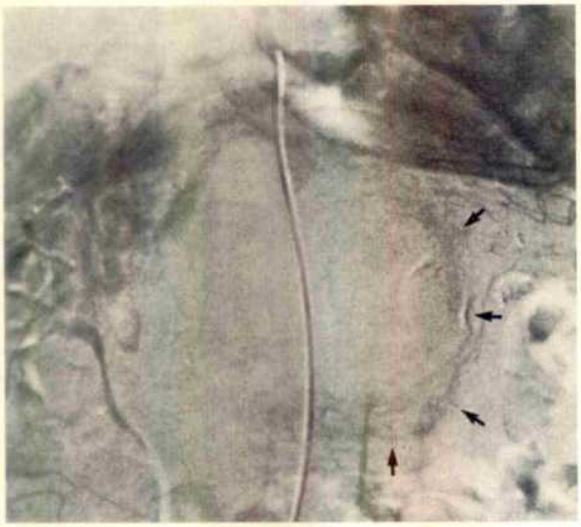

B

FIG. 2.

(A) Right posterior oblique projection of selective superior mesenteric arteriogram shows ileocolic artery (single arrow) and last ileal artery (double arrow) joining in an ileocolic loop in left upper quadrant in the region of the mass. Accessory right colic artery (open arrow) originates from ileocolic artery and confirms the anatomic labelling.

(B) Late venous phase of coeliac arteriogram shows hypervascular rim (arrows) which is fed by omental arteries along border of mass (subtraction film).

DISCUSSION

The ileocolic artery is the only constantly occurring branch of the superior mesenteric artery (Boijsen, 1971; Nebesar *et al.*, 1969). It supplies the terminal ileum, appendix, caecum and proximal ascending colon. The ileocolic loop, formed by the ileal branch of the ileocolic artery and the last ileal branch of the superior mesenteric artery, can be found in about 75% of anatomic dissections and 60% of superior mesenteric angiograms. In our case it was only after persistent effort to clarify the anatomy of the superior mesenteric circulation using the ileocolic artery and ileocolic loop as landmarks that the correct diagnosis could be made. We believe that exact delineation of arterial anatomy, frequently a tedious process, is well worth the effort.

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Short communication

A system for the automated diagnosis of abnormality in breast thermograms

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Thermography has been proposed as a method of screening for early breast cancers in apparently well women (Feasey *et al.*, 1975). A rapid, automated means of diagnosing abnormality in thermograms would be less expensive than visual interpretation in a large scale screening programme (Ziskin *et al.*, 1975; Evans *et al.*, 1976). Towards this end, a Barr and Stroud IR11 thermography unit has been interfaced to a Varian 620L minicomputer system and software developed to analyse breast thermograms. A very simple technique for obtaining the breast outline has been devised, and criteria for abnormality are being investigated.

The IR11 unit operates over a 10°C temperature range set at 25.8°C to 35.6°C; the scanner incorporates a black body reference and has a fixed focal length. An 80-line picture, each line containing 120 picture points, is input to the computer memory. Each picture point contains the calibrated temperature of a 3×3 mm segment of the scanned scene area. These temperatures are digitized in 0.2°C steps by means of an analogue to digital converter incorporated in the IR11 unit and are available as a 10-bit binary coded decimal signal changing every 65 μs. All the information is, in fact, contained in 8 bits, so, in order to save space in the computer memory, the temperatures of two adjacent segments are stored in a single 16-bit computer word. The picture is acquired in one second and is stored together with the patient's name and unit number on magnetic tape, and then analysed. Parameters necessary for diagnosis are still under investigation and those currently available include:

(a) the mean of the average line temperatures over each breast;
(b) the number of segments on each breast with a temperature of at least 1°C above (a);
(c) the maximum temperature and corresponding contralateral temperature;
(d) the areolar temperatures;
(e) combined thermal and geometric asymmetry coefficients.

If requested, high quality hard copy images can be printed out in a few seconds on a Statos electrostatic plotter; grey scale and isotherm formats are available.

After cooling under standard conditions (Feasey *et al.*, 1970) the patient is seated in front of the scanner and the thermographer dresses the patient in an aluminium foil bib fitting between and underneath the breasts (Fig. 1). The top of the bib is adjusted to coincide with the top of the breasts and the nipples are also marked with small reflecting squares. Since the foil has a low emissivity, the nipples and the edges of the breasts are clearly defined as shown in Fig. 2 and can be recognized by a simple computer program. Setting up for the examination typically takes about four minutes; tests have demonstrated that the foil does not significantly perturb the patient's thermal pattern in this time. The picture is acquired and the analysis is completed in less than a minute. Thus, with adequate cooling facilities, the present system would be capable of screening about ten women per hour; this figure could be proportionately increased by interfacing several scanners to one computer, until the computer was analysing thermograms "full time".

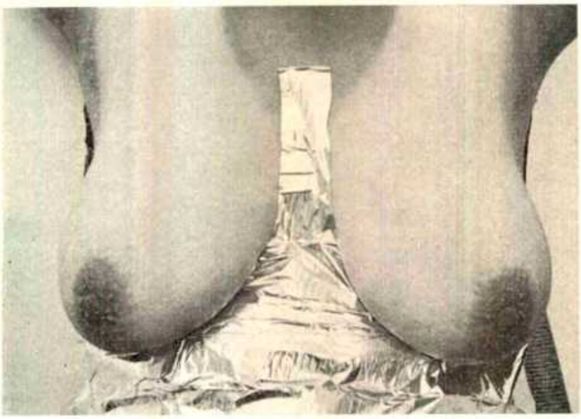

FIG. 1.

Patient wearing an aluminium foil bib.

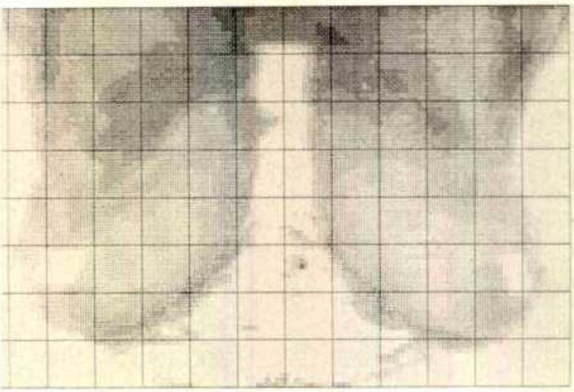

FIG. 2.

Computer-generated thermogram of the patient in Fig. 1 wearing the bib and nipple markers.

Changes in a patient's characteristic thermal print may be significant (Stark, 1976), so a facility for automatically comparing each thermogram with the patient's previous thermograms would be of considerable use. With the system described above, the superposition and comparison of two thermograms would be rapid. A patient faces the scanner directly and is a fixed distance away, so the two images being compared would be of the same size; breast top, centre-line and nipple locations are already calculated in the analysis program, so the images could be superimposed directly. With a rapid-retrieval storage system, it is estimated that the total diagnosis time, *i.e.* analysis of the patient's present thermogram and comparison with the last thermogram on record, would not exceed one minute.

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Book review

Pituitary and Parapituitary Tumours. By J. Hankinson and M. Banna, pp. ix+217, illus., 1976 (W. B. Saunders Co. Ltd), £17·50.

This book is one in the excellent series devoted to major problems in neurology. Lesions affecting the pituitary gland impinge upon several disciplines and most cases are managed best by a co-ordinated team of specialists. This book contains a series of essays all contributed by the group managing these lesions in Newcastle upon Tyne. Despite multiple authorship there is only sufficient overlap to emphasize the significance of the findings of one expert to another.

Most radiologists will learn a great deal from the excellent chapters dealing with non-radiological features and it is refreshing that Mohamed Banna, who has become a superspecialist in this field, has written not only the chapter on neuroradiology but also those on embryology and anatomy, and on pathology and clinical manifestations.

In the radiology section classical teaching is augmented by material from extensive personal reviews of large series of cases. Normal radiological appearances and those found in each type of lesion are well described and illustrated and there is an extensive review of the relevant literature, but neuroradiologists will be disappointed. Relatively large lesions are illustrated and there is no discussion on the difficulties of diagnosing small tumours and on the limitations of the various techniques.

Understandably the author's experience with computed tomography was limited at the time of writing, but the brief mention and illustrations of the method at least suggest that it should occupy the important place it now holds in diagnosis. The value of conventional angiography for showing vascular lesions is stressed and the unsatisfactory yield in tumour diagnosis is mentioned, yet high magnification angiography combined with subtraction which gives much better results is not suggested as a routine, nor illustrated. The use of multi-directional tomography in both examination of the sella and in pneumoencephalography, to obtain the high resolution necessary to detect some small tumours without resorting to exploratory craniotomy is not specifically mentioned.

The book describes neuroradiological practice in most British centres and is recommended to general radiologists and to those commencing the study of neuroradiology, as a good review of the whole subject of pituitary and parapituitary tumours. The omissions reflect the rapid progress of neuroradiology and our inability to replace outdated machinery with suitable apparatus as it becomes available. I hope a second edition of this excellent little book will include these advances.

B. E. KENDALL

1977, *British Journal of Radiology*, *50*, 233–234 MARCH 1977

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

SPOILT FILMS IN X-RAY DEPARTMENTS

Publication of the survey undertaken by R. J. Berry and R. Oliver (May, 1975) coincided with the installation of a Du Pont Cronex Daylight Chest Changer at the Wollongong Hospital which we hoped would reduce our proportion of spoilt films.

All four departments surveyed by Berry and Oliver are known to one of us (A. McK). The Wollongong Hospital, apart from its 500 bed size, corresponds most closely to the district general hospital of their survey; approximately 30,000 examinations are performed each year.

Many factors play a part in film wastage and the undesirable repeat irradiation of patients. Among the causes named by Berry and Oliver we note that 11% of film wastage in the teaching hospital, was due to non-contributory films. These could be discards from an angiographic series, or extra films taken by a teaching hospital radiographer in case the extra view might help. We consider a film to be waste when an exposure is repeated and the original film discarded before the end of the examination. We do not include films discarded at a later stage by a radiologist, because even an apparently non-contributory film does contribute by its very negativity. One could consider the abdomen film showing two functioning kidneys at the end of an aortogram to be non-contributory to the aortogram, and similarly the routine chest film taken for barium patients does not contribute to the meal, but does have great use.

We note also that the Accident and Emergency Department does not quote positioning errors as a significant cause of wastage. Mal-positioning is one of our major causes of waste, partly due to our policy of staff rotation, which increases the frequency of patient rotation. It does, however, remind us that the greater the frequency with which a particular task is performed, the lower the error rate.

The presence of student radiographers also increases the rate of error even under the close supervision in a good department, and this is reflected, along with economic pressures in the low spoilage rate for the private nursing home.

Persistent and recurrent machine faults occur with much of our apparatus, but we agree with Berry and Oliver that this rarely causes an exposure to be repeated. None of our machines is equipped with automatic exposure control or anatomic programmed radiographic facility.

It is our opinion that in a public hospital where economics play a less direct part than in private practice the percentage of spoilt films is directly proportional to the enthusiasm and level of self criticism of the staff of the X-ray Department. We try to maintain high standards of radiography and radiology. Many films are rejected in our department which might be accepted elsewhere, and our standards remain lower than they should.

Film wastage is regularly monitored in Wollongong, and we stress that no member of the staff other than the writers was aware of the Berry and Oliver survey until our figures which we quote below had been collected.

The installation of the chest changer in May, 1976 prompted us to keep separate figures for wastage in this room, these figures are given in Table II. Table I gives figures for the other three rooms. In Table I, a four week period is quoted to minimize the possible effect of marginal error in stock-taking. This error does not arise in Table II.

TABLE I

FOUR WEEK PERIOD. THREE ROOMS

		Film usage	Wastage	Percentage
Total		14,993	1464	9.76
Film size	Common use			
24 × 30	Most used	5265	464	8.81
18 × 24	Extremities, children, gall bladder	3995	514	12.86
18 × 43	Lower limb	550	72	13.09
15 × 40	Spines	533	17	3.19

TABLE II

TWO WEEKS. CHEST ROOM

	Usage	Wastage	Percentage
Total	1277	47	3.68
SOURCE OF WASTAGE:			
Radiographer error			79
Machine fault (film lost or spoilt in transfer or processor)			8.5
Machine testing, cleaning, and demonstrating to staff and visitors.			12.5*

*This figure is now down to negligible level.

The marked difference in wastage rates between different film sizes reflects the frequency of positioning error in the examination of our trauma patients. Positioning error in chest radiography should be minimal and the radiographer error quoted in Table II is almost exclusively exposure fault.

Combining Tables I and II we show an overall wastage rate of 8.88% which is higher than Berry and Oliver's figure, but of the same order of magnitude. We consider that their figures and ours give a good representation of the level of film wastage, and therefore of additional radiation to patients.

Table II shows that 2.8% of film is wasted by exposure error. This could be eliminated by the widespread use of automatic exposure control and anatomic programmed radiographic facility. Further reduction in waste would undoubtedly occur because the radiographer would then be able to concentrate all his attention on positioning and deciding which views would be best suited to show the pathology. Berry and Oliver suggest that the reduction in radiation and film wastage resulting from automated machines is not economical. The total expenditure on film in 1975 in Wollongong was $A33.395, the wastage rate of 8.88% represents $A2,965, and a saving of 2.5% total film would save $A835. Ionization chambers, at a cost of $A3000, or simple phototimers at considerably less, would pay for themselves in film alone within the normal life span of an X-ray machine, and the reduction in additional radiation is obviously desirable.

Finally, we do not believe that a reduction of film wastage, by our definition below about 5% is likely to be achieved without sacrificing radiographic quality and diagnostic accuracy.

Yours etc.,
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REFERENCE

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The Editor—Sir,

High Kilovoltage Techniques and the Choice of Optimal Filtration in Xeroradiography

The widespread interest among radiologists and clinicians concerning radiation dosage to the patient in xeroradiography prompts us to point out some relevant factors affecting this issue.

A previous publication on patient dosage (Boag *et al.*, 1976) showed that the use of an applied tube voltage of 122 kV (effective) resulted in an incident skin exposure similar to that of comparable conventional techniques employing X-ray film with intensifying screens (but at lower kilovoltages). At that time 122 kV (effective) was the maximum available to us. However, more recently we have had regular access to equipment used for general xeroradiography up to 150 kV (nominal)* and occasional access to other equipment operating at tube voltages up to 200 kV (nominal)†.

As may have been expected, we have found that these higher kilovoltages could be employed to reduce incident skin exposure. In addition, however, at these voltages the exposure was further reduced by the use of additional filtration, without corresponding loss of diagnostic quality in the xeroradiograph. Indeed, for some examinations the modification of the "edge-enhancement" associated with higher filtration was advantageous. For example, we have used a composite (radiotherapy) filter equivalent to one millimetre of copper to obtain satisfactory xeroradiographs both of the chest and of P.A. projections of soft tissues in the neck region, whilst reducing the incident skin exposure by a factor of approximately two.

Similar techniques have been applied to cephalometric xeroradiography (Davis *et al.*, 1976). Work is therefore in progress to examine the extent to which patient dosage can be reduced by the application of these higher kilovoltages and to correlate the changes in image quality associated with a range of added filtration, for several anatomical sites.

Since image formation is dependant on many variables and assessment of image quality is made subjectively, it is incumbent upon radiological teams to establish the optimal parameters for each examination.

The purpose of this letter is to draw attention to the ways by which patient exposure can be lowered in xeroradiography by applying high kilovoltage techniques and also by placing heavier filtration in the X-ray beam.

Higher voltage generators are becoming more widely used and, in our opinion, it is most desirable that centres with the necessary equipment and staff should assess these variables more precisely and thereby provide urgently needed data in a field which remains little explored.

Yours, etc.
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Boag, J. W., Stacey, A. J., and Davis, R., 1976. Radiation exposure to the patient in xeroradiography. *British Journal of Radiology*, *49*, 253–261.

Davis, R., Binnie, W. H., Cawson, R. A., Reed, R., and Stacey, A. J., 1977. The rôle of xeroradiography in cephalometric radiology. *Journal of Dentistry*, *5*, 32–38.

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*Siemens, Gigantos generator with BI/30/50R X-ray tube.

†Elema–Schönander, Triplex Optimatic 1023 generator with BI/200/20/50 s. X-ray tube.

The Editor—Sir,

Deconvolution Analysis of the Scintillation Camera Renogram

The above paper (Kenny *et al.*, 1975) discusses an interesting approach with potential application to renal evaluation in terms of a distribution of transits times within the kidney. The fundamental assumptions involved are that the kidneys can be viewed as a linear time invariant system during the period of examination (which can usually be accepted) thus justifying the Laplace transform methods of analysis which were employed. However, I take exception to the position taken by the authors where it was stated that the "removal of Hippuran from the blood by the kidneys gives rise to a biexponential blood clearance curve of the same shape as the renal input function".

The cardiac time : activity curve represents the distribution of Hippuran within the circulatory system and does not represent the renal input function. The renal input function is given by the negative time derivative of the cardiac curve which can be obtained from a least squares fit of this curve. Since the amount of Hippuran entering the kidneys depends upon the amount leaving the circulatory system, the input to the renal system will be a function of how the cardiac curve is changing. In addition, the renal input function is a positive valued function which, when considered collectively, infers the negative time derivative of the cardiac curve.

If it is assumed that the Hippuran distribution in the blood can be represented by a two compartment model (DeGrazia *et al.*, 1974) the above argument can be demonstrated mathematically.

$$\begin{tikzcd}
\left[X_2\right] \arrow[r, shift left, "K_2"] & \left[X_1\right] \arrow[l, shift left, "K_3"] \arrow[r, "K_1"] & \text{to the renal system}
\end{tikzcd}$$

let X_1, X_2 be the quantities in two compartments
K_1, K_2, K_3, corresponding rate constants
and $r(t)$, observed circulatory activity.

The differential equations describing this system are

$$X_1(t) = -(K_1+K_3)X_1(t)+K_2X_2(t) \quad \ldots\ldots\ldots\ldots (1)$$

$$\dot{X}_2(t) = K_3X_1(t)-K_2X_2(t) \quad \ldots\ldots\ldots\ldots (2)$$

with arbitrary initial conditions.

The observed circulatory activity is

$$r(t)=X_1(t)+X_2(t) \qquad (3)$$

Differentiating equation (3) and substituting equations (1) and (2) into that result yields

$$\frac{d}{dt}r(t)=-K_1X_1(t) \qquad (4)$$

This result, upon closer examination, represents the quantity of Hippuran leaving the circulatory system. Then, the negative of equation (4) would represent the quantity of Hippuran entering the renal system, or the renal input function. If the cardiac time: activity curve is given by an equation of the form

$$r(t)=Ae^{-at}+Be^{-bt}$$

then the correct expression for the renal input function in the author's notation should, therefore, be given by

$$i(t)=Aae^{-at}+Bbe^{-bt}$$

Yours, etc.,
C. APPLEDORN

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REFERENCES

DEGRAZIA, J. A., SCHEIBE, P. O., JACKSON, P. E., ZOLTAN, J. L., FAIR, W. R., VOGEL, J. M., BLUMIN, L. J., 1974. Clinical applications of a kinetic model of Hippurate distribution and renal clearance. *Journal of Nuclear Medicine*, *15*, 102–114.

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THE EDITOR—SIR,

DECONVOLUTION ANALYSIS OF THE SCINTILLATION CAMERA RENOGRAM

We would like to thank Dr. Appledorn for his comments on the above paper. However, we do not accept equation 3 of his letter describing the observed circulatory activity which should be

$$i(t)=fX_1(t)+(1-f)X_2(t)$$

where f represents the fractional contribution from the blood within the region of interest. As indicated in the original paper, the value of f depends on where the region of interest for measuring circulatory activity is chosen. In the technique described, the region used was taken over the heart and therefore f approximates to unity. Making this approximation the quantity of Hippuran leaving the circulatory system for the kidney becomes

$$di(t)/dt=-K_1X_1(t)=-K_1i(t)$$

and the quantity of Hippuran entering the kidney is $K_1i(t)$ which in our original notation is proportional to

$$Ae^{-a_1t}+Be^{-a_2t}$$

The assumption made in this argument that the cardiac region contains no extravascular Hippuran space is, of course, an approximation. However, it can be corrected by subtracting a suitable background contribution from $i(t)$ (Fleming, 1977).

Yours, etc.,
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REFERENCE

FLEMING, J. S., 1977. Measurement of hippuran blood clearance using a gamma camera. (In preparation.)

THE EDITOR—SIR,

RADIOPHARMACEUTICAL DOSIMETRY

At a symposium on Radiopharmaceutical Dosimetry at Oak Ridge, attended by us in early 1976, several speakers drew attention to the pressing need for the collection of biokinetic distribution data in order to improve the accuracy of radiation dose calculations, both for healthy individuals and patients.

More information of this type should become available with the increase in "dynamic" activity-time studies in nuclear medicine, and we would ask you to make this need known to your readers.

Roger J. Cloutier, of Oak Ridge Associated Universities, has agreed to collate this information, which should be sent to him at ORAU, PO Box 117, Oak Ridge, Tennessee 37830, USA.

Yours etc.,
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THE EDITOR—SIR,

LYMPHOCYTE RESPONSE TO PHYTOHAEMAGGLUTININ AFTER *IN VITRO* IRRADIATION

With reference to the response of *in vitro* irradiated human lymphocytes to phytohaemagglutinin (PHA), in agreement with data obtained by Ilbery *et al.* (1971), Braeman and Moore (1974), and Yosef and Nias (1976), we have observed a decrease in the transformation index to 95, 56 and 38% of control (non-irradiated) lymphocytes following incremental doses of 625, 1250, and 2500 rad respectively.

The variability in the extent to which the lymphocyte response is depressed can be ascribed to differences both in the procedures followed by the various authors and in the criteria according to which the transformation index was evaluated (*i.e.* morphological criteria or scintillation counting).

It is interesting to note that, at variance with results obtained with PHA, antigen-induced mitogenesis or that in mixed lymphocyte culture (MLC) appeared to be severely inhibited even following low radiation doses. Peripheral blood lymphocytes from eight healthy adult donors were examined after separation on a Ficoll-Hypaque gradient. The response to stimulation with specific antigens (Candida) or with allogenic lymphocytes was evaluated by measuring the uptake of ^{3}H-thymidine from seven-day-old cultures.

1977, *British Journal of Radiology*, *50*, 236

TABLE I

Lymphocyte response to Candida Albicans (Hollister-Stier Laboratories: 2·5µl/ml) and to allogenic lymphocytes following incremental radiation doses. Results are expressed in radioactive counts per minute (c. p. m.) and represent the mean values ±s.e. obtained with lymphocytes from eight healthy adult donors examined under the same experimental conditions.

Candida Albicans

Unstimulated lymphocytes	Stimulated non-irradiated lymphocytes	Stimulated irradiated lymphocytes		
		2500 rad	1250 rad	625 rad
1042±323	7322±2300	418±86	628±378	475±198

Mixed lymphocyte culture

	2500 rad	1250 rad	625 rad
AB_r—BA_r	10606±2876	6449±2447	7036±1859
AA_r—BB_r	849±324	980±380	753±306
A_rB_r	544±243	574±62	607±113

AB_r—BA_r: stimulation of donor A by donor B irradiated lymphocytes and *vice versa*.
AA_r—BB_r: background of non-specific activity of A and B.
A_rB_r: efficacy of radiation induced inhibition of A and B.

Table I clearly shows that an almost complete suppression in lymphocyte reactivity is evident after a dose of 625 rad. This finding could be related to the existence of lymphocyte subpopulations endowed with distinctive radiosensitivity. An alternative explanation would be provided by a radiation-dependent damage which is made evident after rather prolonged time intervals such as those chosen in order to evaluate the response to specific antigens and in MLC.

Yours, etc.,
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Braeman, J., and Moore, J. L., 1974. The lymphocyte response to phytohaemagglutinin after *in vitro* irradiation. *British Journal of Radiology*, *47*, 297.

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Yosef, H. M. A., and Nias, A. H. W., 1976. The lymphocyte response to phytohaemagglutinin after *in vitro* irradiation. *British Journal of Radiology*, *49*, 295.

1977, *British Journal of Radiology*, *50*, 237–238 MARCH 1977

Proceedings of The British Institute of Radiology

Abstracts of papers read at the Radiobiology Work-in-Progress meeting held in the Reid Knox Hall, Institute House, 32 Welbeck Street, London W1 on Friday, November 19, 1976

Some radiobiological consequences of mycoplasma contamination in tissue culture, by Beulah M. Cullen and Luisa Manjil.
Relative biological effects of X and gamma rays with fractionated irradiations of *Vicia faba* roots, by M. T. Khokhar, R. Oliver and E. W. Emery.
Mast cell response in irradiated lung, by Elizabeth L. Travis.
A possible mechanism for radiation myelopathy, By B. M. Hubbard.
The effects of cytotoxic agents on intestinal stem cells, by T. A. Boarder and N. M. Blackett.
Patterns of vasculature in two related pairs of rat tumours and their relevance to radiotherapy, by P. Falk.

SOME RADIOBIOLOGICAL CONSEQUENCES OF MYCOPLASMA CONTAMINATION IN TISSUE CULTURE

By Beulah M. Cullen and Luisa Manjil

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Cells of the mouse Ehrlich ascites carcinoma grown *in vitro* became contaminated with an arginine-splitting mycoplasma. The first sign of trouble appeared when the slopes of the radiation survival curves of the cells assayed by cell colony forming ability became extremely variable; eventually it became impossible to grow colonies at all. Experiments on the feeder cell requirement showed that, whereas for clean cells the maximum plating efficiency was obtained within a range of 5×10^4 to 3×10^5 feeder cells in a 5 cm dish, contaminated cells would only produce colonies in the presence of between 10^4 to 2×10^4 feeder cells. Doubling the concentration of arginine in the medium allowed contaminated cells to grow with maximum plating efficiency within an increased range of 10^4 to 4×10^5 feeder cells. The mycoplasmas were apparently behaving as feeders, reducing the requirement for added feeder cells, but also depleting the medium of essential arginine. It seems likely that the variability in slope of the survival curves was also caused by arginine deficiency for the following reason. The number of cells added to each Petri dish was increased with the dose of radiation to be given, to allow similar numbers of cells to survive in each dish; there would be a concomitant increase in mycoplasma concentration. Cells surviving the radiation would therefore have a probability of succumbing to arginine deficiency, which would increase with dose, so producing an artificially steep survival curve. The cells were eventually decontaminated by passaging them through a mouse as an ascites tumour.

RELATIVE BIOLOGICAL EFFECTS OF X AND GAMMA RAYS WITH FRACTIONATED IRRADIATIONS OF *VICIA FABA* ROOTS

By M. T. Khokhar, R. Oliver and E. W. Emery

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The investigation set out to examine how the biological effectiveness of 250 kV X rays relative to ^{60}Co γ rays in reducing the growth of bean roots varies with the size of the dose. The effect observed was the elongation of the roots in a period of ten days relative to the unirradiated controls (G10). In order to make observable the effect of small doses, comparable total doses were given in varying numbers of equal fractions, separated by 24 hours to allow recovery from sub-lethal damage, and with the beans maintained at 3·5°C to prevent cell proliferation.

It is generally accepted that reduction of cell growth is an expression of cell-sterilization in the meristem (Gray and Scholes, 1951) and it is probable that the cell survival curve has a definite initial slope, such as might be expected to result from cell killing by a single radiation event. On this view it is likely that X rays, the more densely ionizing radiation, would produce the greater initial slope to the survival curve, and so show an RBE that increases as the dose given is reduced. Experiments were conducted with irradiations in 1, 3, 6 and 12 fractions, producing G10's ranging from 0·65 to 0·15. The smallest dose fractions were only 17 rad. The observed RBE was virtually constant at 1·2 from 200 to 80 rad/fraction, and thereafter increased to 1·5 at 17 rad per fraction, in accordance with the above hypothesis.

REFERENCE

GRAY, L. H., and SCHOLES, M. E., 1951. The effect of ionizing radiations on the broad bean root. *British Journal of Radiology*, *24*, 285–291.

MAST CELL RESPONSE IN IRRADIATED LUNG

By Elizabeth L. Travis

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Mast cells have been implicated in the pathogenesis of oedema and fibrosis after many types of trauma, including irradiation. The aim of this study was to determine qualitative and quantitative changes in mast cell distribution after pulmonary irradiation.

The right thorax of Sprague-Dawley rats was exposed to 0·5, 10, 20 or 40 gray of X rays. Animals from each group were sacrificed at 2, 4, 6, 8, 12 and 72 weeks post-exposure and tissues from both lungs studied by light and electron microscopy. Tissues for light microscopy were stained with haematoxylin and eosin, Azure A at pH 1·5 for mast cells, Masson's trichrome for collagen, and Gordon-Sweet's reticulin method. Tissues for electron microscopy were fixed by standard glutaraldehyde-osmium techniques and thin sections stained with uranyl acetate-lead citrate.

Lungs exposed to 5 and 10 gray exhibited no pathological changes; mast cells were located in pleural, peribronchial, and perivascular sites, consistent with controls. An early pneumonitis progressing to fibrosis was observed in lungs exposed to 20 and 40 gray and an interstitial mast cell infiltrate was present in the alveolar walls. The time of appearance of this infiltrate and the cell numbers involved were dose-dependent. Mast cell degranulation was evident and increased mast cell numbers were present in fibrotic areas. Electron microscopy revealed mast cells in close spatial approximation to fibroblasts with membrane alterations indicative of pinocytosis.

These observations suggest mast cell participation in the radiation induced pneumonitis and fibrotic processes.

A POSSIBLE MECHANISM FOR RADIATION MYELOPATHY

By Bethan M. Hubbard

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Irradiation of the rat cervical cord with single doses greater than 2000 rad results in the development of paralysis of the fore limbs and associated extensive white matter necrosis, after a latent period of several months.

The relative changes in the density of both astrocytes and oligodendrocytes were determined during the latent period after irradiation and were found to be similar. Both cell types showed an initial reduction in density one month after irradiation. There was an apparent recovery at two months but this was followed by a rapid decline in both cell populations between three and four months after irradiation. These changes preceded the onset of paralysis.

Occasional mitotic figures observed in the neuroglia of both normal and irradiated spinal cords and subsequent continuous labelling studies with ^{3}H-thymidine suggest that neuroglia are not a static cell population.

It is concluded that following a dose of 4000 rad the development of white matter necrosis is primarily due to the loss of oligodendrocytes. It is also evident that the glial cell population of the spinal cord has a slow rate of turnover and this accounts for the delayed onset of necrosis.

THE EFFECTS OF CYTOTOXIC AGENTS ON INTESTINAL STEM CELLS

By T. A. Boarder and N. M. Blackett

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The microcolony assay technique developed by Withers and Elkind (1970) was used to study the effects of cytotoxic agents. It was observed that there was no similar pattern of recovery between drugs which have a similar mode of action (*e.g.* S-phase specific agents). Emphasis was given to the study of the S-phase specific cytotoxic agents cytosine arabinoside, tritiated thymidine and hydroxyurea.

Survival curves were obtained immediately after 200 mg/kg cytosine arabinoside and 2 h after 1 mCi ^{3}HTdR (specific activity 23 Ci/m mole), and these were compared to their γ-only control curves. A 60–85% decrease in microcolony surviving fraction was observed, which strongly suggests that a significant proportion of the intestinal clonogenic stem cells, as assayed by this techique, are rapidly-proliferating.

Experiments with cytosine arabinoside show that this drug affords the intestine a large measure of radioprotection when given 12 h before irradiation. The surviving fraction of microcolonies is raised well above γ-controls at this time, and animal survival experiments show that at 1700 R the onset of gut-induced death is delayed only in the 12 h pretreated mice. At lower radiation doses both bone marrow and gut-induced death is prevented.

The high microcolony survival at 12 h after cytosine arabinoside was found to be due to a doubling of D_0 to over 300 R compared with the γ-control value of 140 R. This finding excludes the possibility that age-dependent sensitivity variations caused by synchronization after cytosine arabinoside are responsible for the high microcolony survival. This has previously been suggested by Gillette, Withers and Tannock to explain a similar finding after hydroxyurea administration. Indeed, no evidence from labelling indices was found to suggest the presence of synchrony after hydroxyurea or cytosine arabinoside, and no microcolony peaks were observed at times up to 24 h after hydroxyurea. Split dose experiments at 12 h after cytosine arabinoside reveal no apparent recovery factor (time interval = 8 h) which is thought to be due to masking of recovery by an increasing radiosensitivity brought about by a decreasing D_0 appearing at times after 12 h.

PATTERNS OF VASCULATURE IN TWO RELATED PAIRS OF RAT TUMOURS AND THEIR RELEVANCE TO RADIOTHERAPY

By P. Falk

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Du Cane Road, London, W12

Two methods were used to investigate the patterns of vasculature of the four tumour lines. Thick (200 μm) sections were cut by cryostat and, after staining, a projecting microscope was used to trace the vasculature onto transparent acetate sheets. Each tracing was supported on a sheet of glass and the glass sheets stacked one above another with spacers between to give a three-dimensional model when illuminated from below. Alternatively, after fixation tumours were halved horizontally, the outer half being left embedded in skin, the inner in the abdominal wall. The preparations were stained and dehydrated and then cleared and mounted in Resin No. 4116 (B.I.P. Chemicals Ltd., P.O. Box 6, Warley, Worcs.). In both methods blood was revealed by staining with benzidine.

The four tumour lines used were relatively anaplastic fibrosarcomas, the radiation responses of which had already been intensively investigated. They were: RIB$_5$, originally induced by Thomlinson by subcutaneous injection of benzopyrene, RIB$_5$C derived from it by McNally by culturing the cells *in vitro* over a period of 12 months, SSB$_1$A and SSB$_1$B derived from a single spontaneous tumour, the two lines being separated by their different growth rates. Volume doubling times at 9 mm diameter are: RIB$_5$ 1 day, RIB$_5$C 12 days, SSB$_1$A 1½ days, and SSB$_1$B 4½ days. Massive central necrosis occurs in RIB$_5$ and SSB$_1$A when they exceed about 20 mm in diameter; islands of necrosis occur in RIB$_5$C at the same diameter; necrosis is unknown in SSB$_1$B. It was observed that when RIB$_5$ and SSB$_1$A were sectioned, the sections curved into the shape of a saucer, indicating a pressure difference between the centre and the circumference; sections of RIB$_5$C and SSB$_1$B remained flat. Consequently the two former are regarded as *tense* tumours, the two latter as *lax*.

Each tumour line was found to have its characteristic pattern of vasculature, the two lax tumours showing a pattern of central supply and drainage, the main artery and vein, both with a muscular investiture, entering together at the base and showing fairly rich arborescent branching, while the two tense tumours exhibited peripheral supply and drainage, but of widely different patterns. The causes of this difference between the two tense tumour lines were examined and were in part ascribed to the investiture of collagen on the vessels of SSB$_1$A, which it is unique in possessing. It would be expected that the lax tumours with their central supply and drainage would have a more even supply of oxygen to their cells than the tense with their peripheral supply and drainage. In the tense, as the tumour grows, hypoxia seems certain to develop in the central area; in the lax it may occur, but there is no certainty that it will. The radiation data summarized by Howlett *et al.*, 1975, was examined and was shown substantially to give support to this hypothesis.

REFERENCE

HOWLETT, J. F., THOMLINSON, R. H., and ALPER, T., 1975. A marked dependence of the comparative effectiveness of neutrons on tumour line, and its implications for clinical trials. *British Journal of Radiology*, *48*, 40–47.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

B.I.R. LIBRARY

The opening of the Institute's house for members to use the Library on Saturday mornings has been discontinued through lack of support. However, arrangements would be made for the Library to be opened between 10.00 a.m. and 1.00 p.m. on a Saturday if prior notice was given. Telephone 01–935 6237 or write to The General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

9TH INTERNATIONAL DIAGNOSTIC COURSE IN DAVOS SWITZERLAND—HEART AND LUNG

Sponsored by European Association of Radiology. To be held on March 27–April 2, 1977.

Further information and registration please contact IDKD 9, Postfach 2132, CH–8028 Zurich, Switzerland.

THE BRITISH INSTITUTE OF RADIOLOGY ANNUAL CONGRESS AND SCIENTIFIC EXHIBITION

To be held on April 14–15, 1977 at the R.I.B.A., 66 Portland Place, London W1. Papers presented will include the "Silvanus Thompson Memorial Lecture" entitled *The present state of computed tomography and its future*, by Mr. G. N. Hounsfield, C.B.E., of EMI Central Research Laboratories.

Further information and registration from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

RADIATION PROTECTION: AN EXAMPLE OF ACTION AGAINST MODERN HAZARDS

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P., no. 33, 92260 Fontenay-aux-Roses, France.

THE MACKENZIE DAVIDSON MEMORIAL LECTURE

To be given by Dr. David Ingvar, University of Lund on May 19, 1977 at The British Institute of Radiology.

NEW HORIZONS IN INTENSIFYING SCREEN TECHNOLOGY

An all-day meeting organized by the Industry Committee of The British Institute of Radiology on May 20, 1977 at the Middlesex Hospital Medical School, London, W1. Registration details and information from the General Secretary, The British Institute of Radiology.

EXPERIMENTAL AND CLINICAL APPLICATIONS OF KRYPTON 81M

An all-day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology to be held at the Middlesex Hospital Medical School, London, W1 on June 3, 1977. Registration and details from the General Secretary.

HYPOXIC CELL SENSITIZERS IN RADIOBIOLOGY AND RADIOTHERAPY

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV INTERNATIONAL CONGRESS OF RADIOLOGY

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV International Congress of Radiology, Avenida Churchill 97—5th Floor, ZC 39, 20,000, Rio de Janeiro, Brazil.

1977, *British Journal of Radiology*, 50, 240

Employment of unqualified staff

Issued by R. M. Jordan, Secretary, The Society of Radiographers, 14 Upper Wimpole Street, London W1M 8BN

From time to time Council's attention is drawn to situations where radiography is being undertaken by unqualified staff. Often the problem can be resolved simply by informing the relevant authorities of the problems they may be creating for themselves by using unqualified staff but occasionally these warnings go unheeded.

For instance, over a considerable length of time the Society has written and complained to the Home Office about the practice of allowing prison officers to undertake radiography on prison inmates. Another recent example has been an advertisement in a local newspaper in Plymouth for a State Enrolled Nurse to work in H.M. Naval Base who would also undertake "simple" radiography.

The Society is committed wholly and unequivocally to the principle that radiography is potentially far too dangerous to be carried out by anyone who has not been properly trained and is not a State Registered radiographer. Unfortunately, there is no obligation on private industry to employ qualified radiographers, although most companies will insist on employing qualified staff when told of the inherent hazards, not least those in the field of litigation.

When it comes to government authorities the situation is clearer. The National Health Service has issued regulations governing the employment of radiographers, and since 1964 it has been a condition of employment that all staff employed in the capacity of radiographers must be State Registered; therefore those hospitals who allow and encourage non-radiographic staff to undertake radiography are plainly contravening these requirements, and the Society will take up these instances when they are brought to our attention.

The Society objects most strongly if employing authorities, both within the N.H.S. and outside, persist in employing unqualified staff and Council hopes that members will play their part by not co-operating in any attempt by employers to partially train non-radiographic staff to undertake radiography. If members are approached, they are advised to report the matter to their Regional Representative on Council and to refuse to assist in any way with the training of staff or commissioning of departments which will not be staffed by qualified radiographers. This advice includes those members who may be approached to help with the training of prison officers, dental assistants, nurses, chiropodists, podiatrists, and nurses.

Obituary

Philip Hague Lovell, M.B., B.S., D.M.R.D.

Dr. Philip Lovell, Consultant Radiologist to the Medway and Dartford and Gravesham Districts died on Tuesday, October 5, 1976 at the age of 51.

Son of a general practitioner, his early life was spent in Knutsford and he was brought up in the best traditions of an earlier generation of doctors. His athletic build and ability obtained him places in the school first XV and cricket teams and he maintained his interest in sport after leaving school, representing the Royal Navy at tennis. Amongst his hobbies were stamp collecting, gardening and woodwork.

Philip qualified in November 1949, having trained at the Middlesex Hospital Medical School and then held posts as house physician and house surgeon at the West Suffolk General Hospital, Bury St. Edmunds where he first met his wife Olive. Most of Philip's medical career was spent in the Royal Navy which he joined in February 1951, at first on a short service commission and then on the permanent list until December 1968, having attained the rank of Surgeon Commander. During this time he served in Malaya, Malta and the Suez Canal areas with 42 Commando, Royal Marines. He also held appointments at Devonport, Plymouth and aboard H.M.S. *Ark Royal*. His involvement in radiology commenced in December 1958 when he became a trainee radiologist at the Royal Naval Hospital Plymouth and for some of this training was seconded to the X-ray Department at the Middlesex Hospital. After taking the D.M.R.D. in 1962 he was radiologist at Singapore, Haslar and Plymouth. During a further tour of duty in Singapore he was visiting radiologist to the R.A.A.F. Hospital, Malayasia.

He was appointed Consultant Radiologist to the Medway and Gravesend and Dartford Hospital Groups in May 1969. He was held in great affection by all who worked with him and one cannot recall Philip ever saying an unkind word. His calm and patient manner made him an excellent colleague whose advice was highly valued not only in radiology, but also in administrative and other matters. He showed a special interest in contrast examinations such as myelography and sialography.

Philip became ill in October 1975, requiring a major operation and radiotherapy. After a period of convalescence he returned to work, but became ill again in August of this year. Although well aware of the serious nature of his condition he showed great fortitude, as did his wife and family. Typical of his unselfish nature was the fact that at this time his main concern was for his family.

His great popularity was evident at his funeral which was attended by so many people, including representatives of the Royal Marines as well as the Royal Navy.

With his passing we have lost a trustworthy friend and colleague. Our sympathy is extended to his wife Olive, also their children Robin, Ian and Fay.

S. J. H.

Book reviews

Handbuch der Medizinischen Radiologie (Encyclopedia of Medical Radiology, Vol. 5, part 1—Diseases of the skeletal system) 174

Handbuch der Medizinischen Radiologie (Encyclopedia of Medical Radiology, Vol. 6, part 3—Roentgen diagnosis of the vertebral column) 174

Nuclear Medicine: Report of a joint I.A.E.A./W.H.O. expert committee on the use of ionizing radiation and radioisotopes for medical purposes (nuclear medicine). Technical Report Series 591. 184

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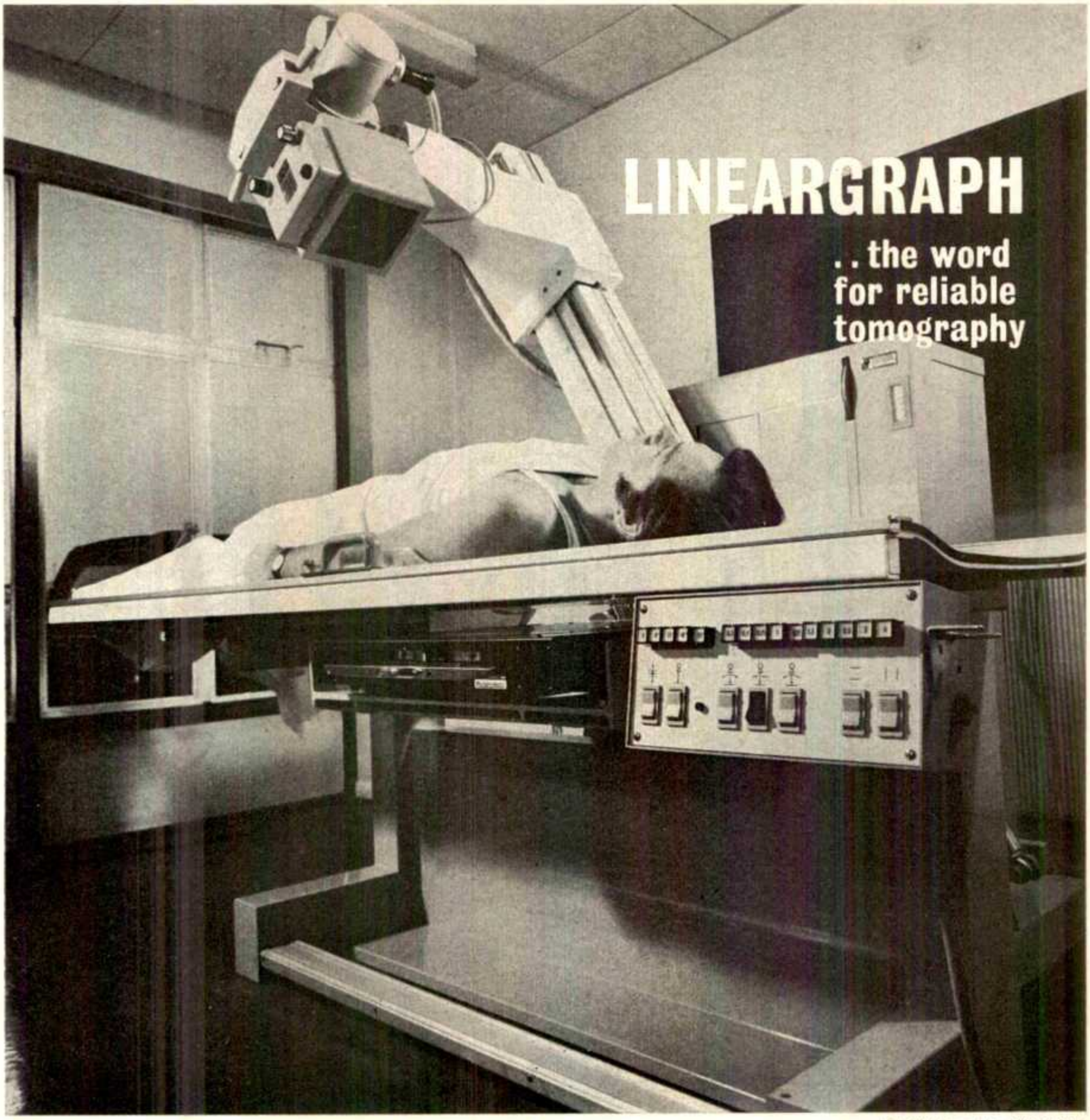

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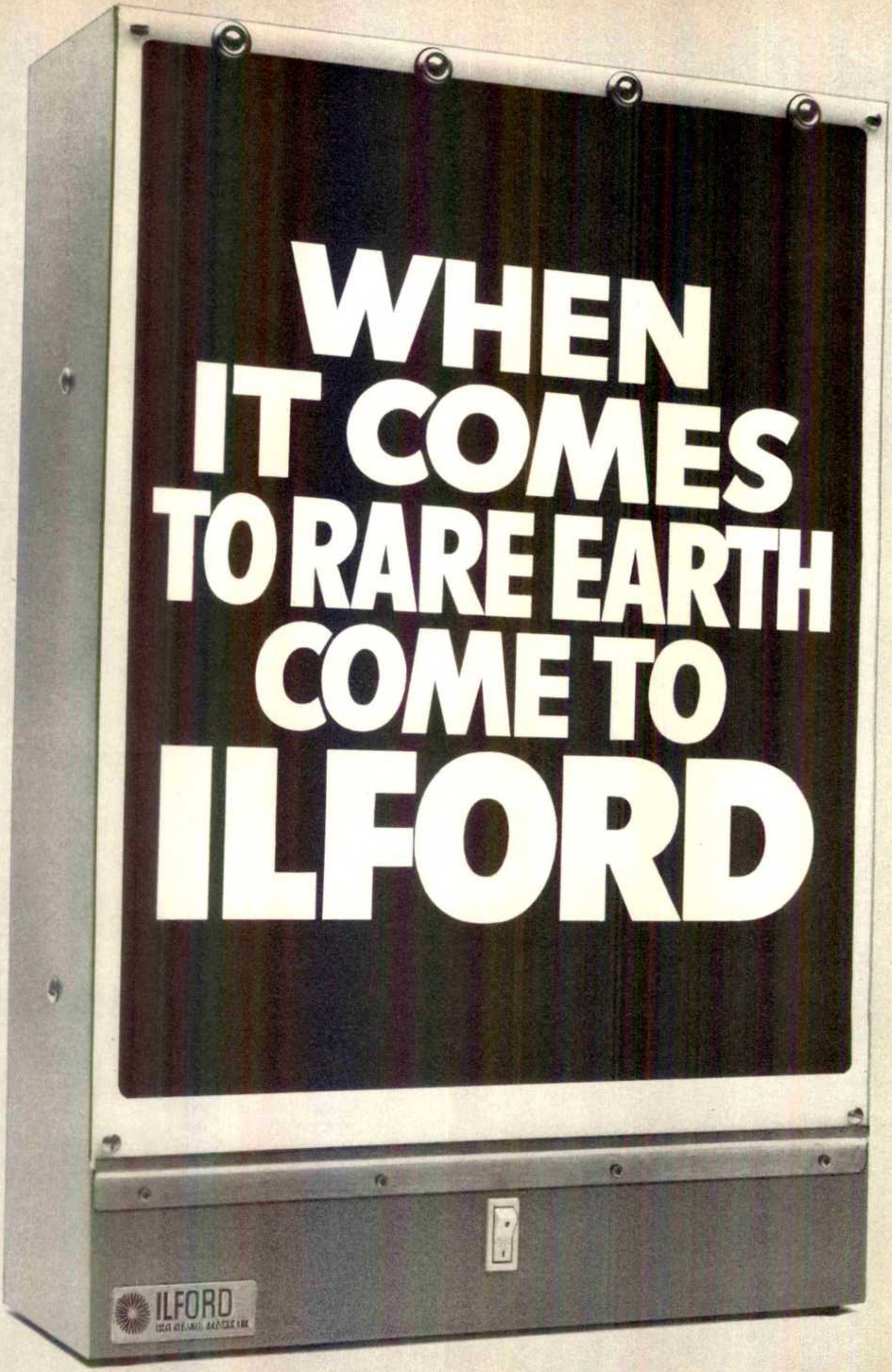
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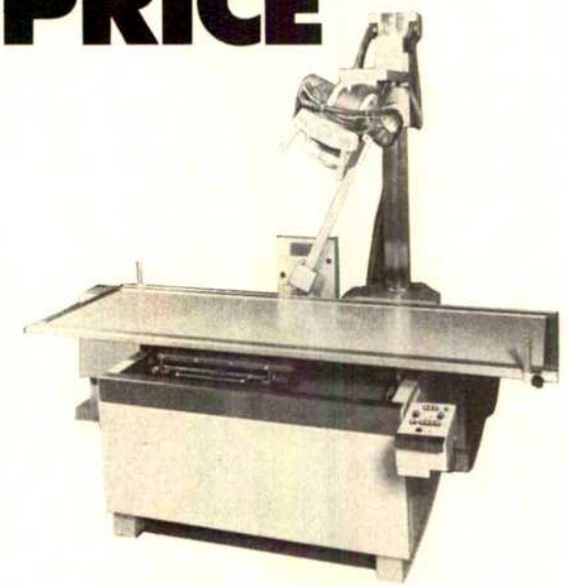

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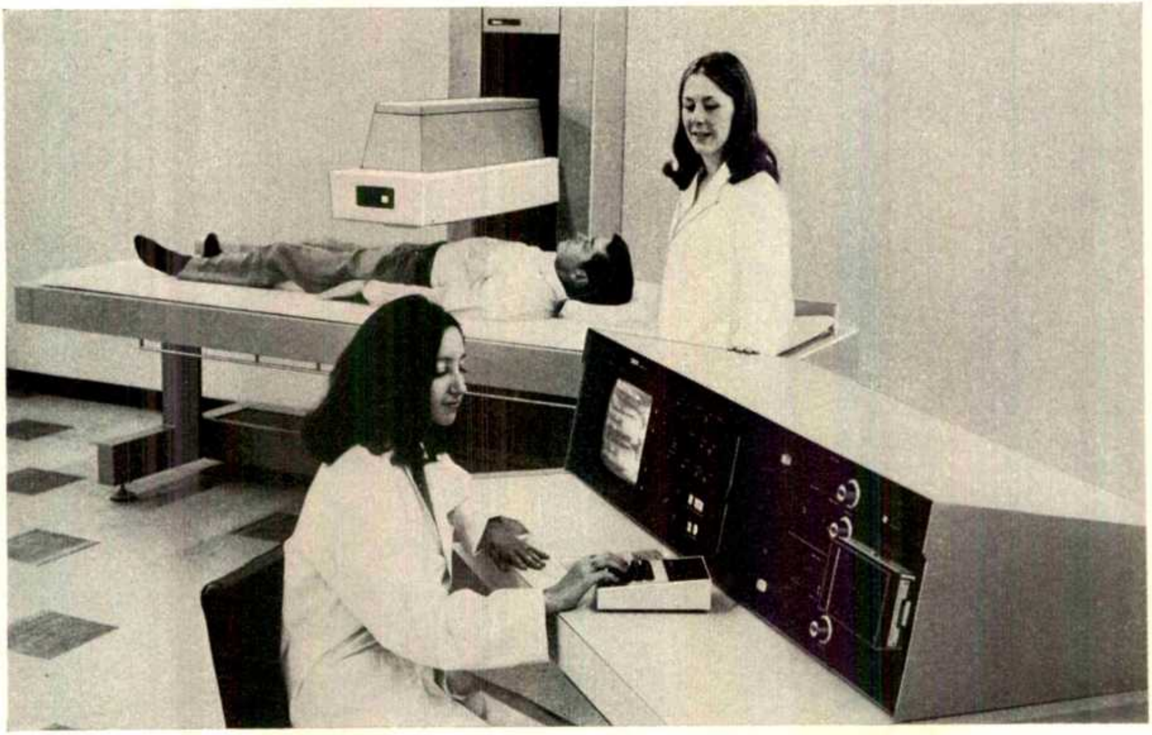

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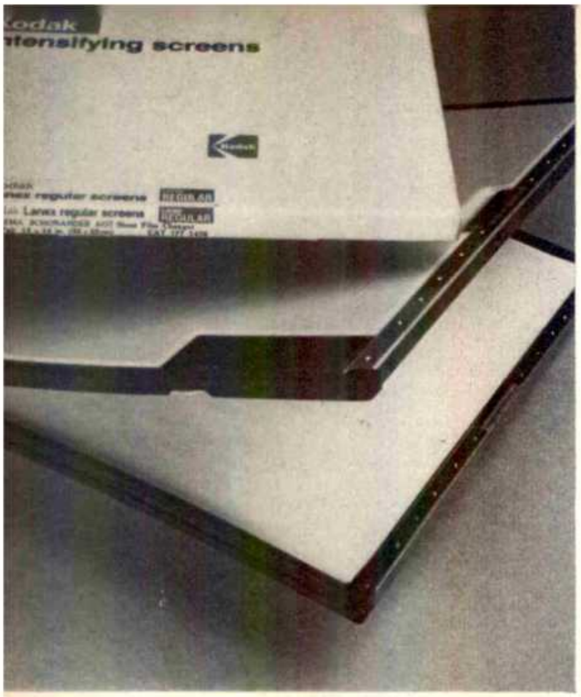

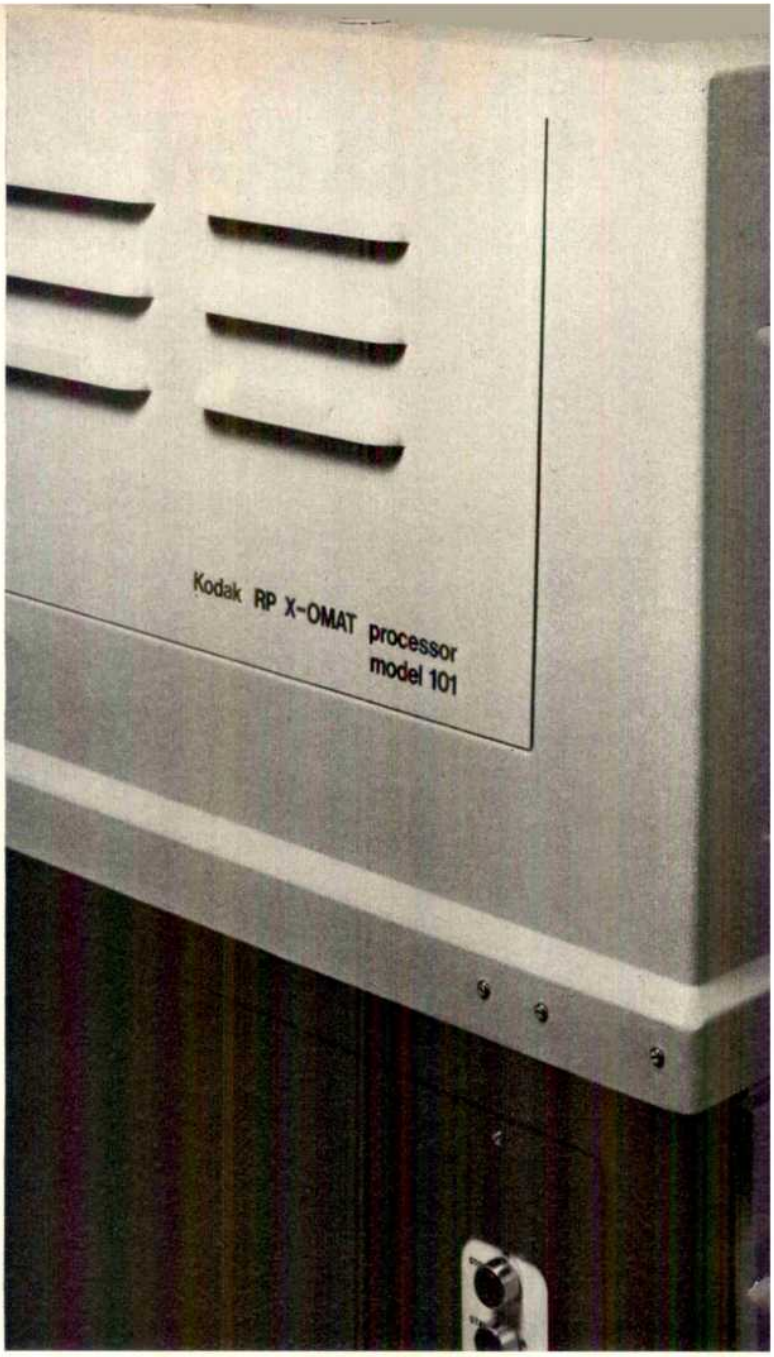

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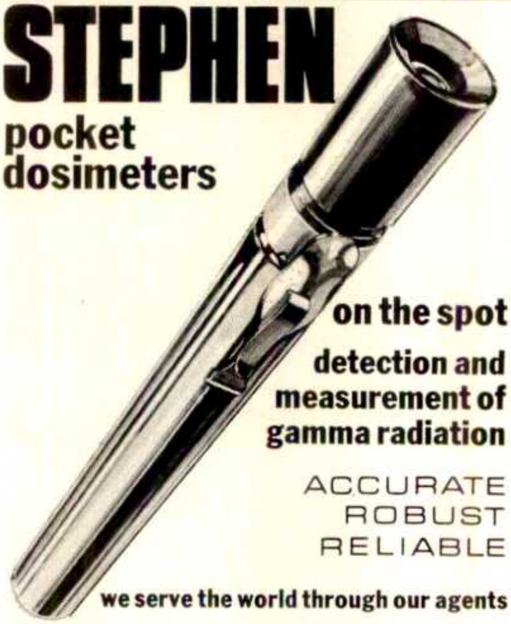

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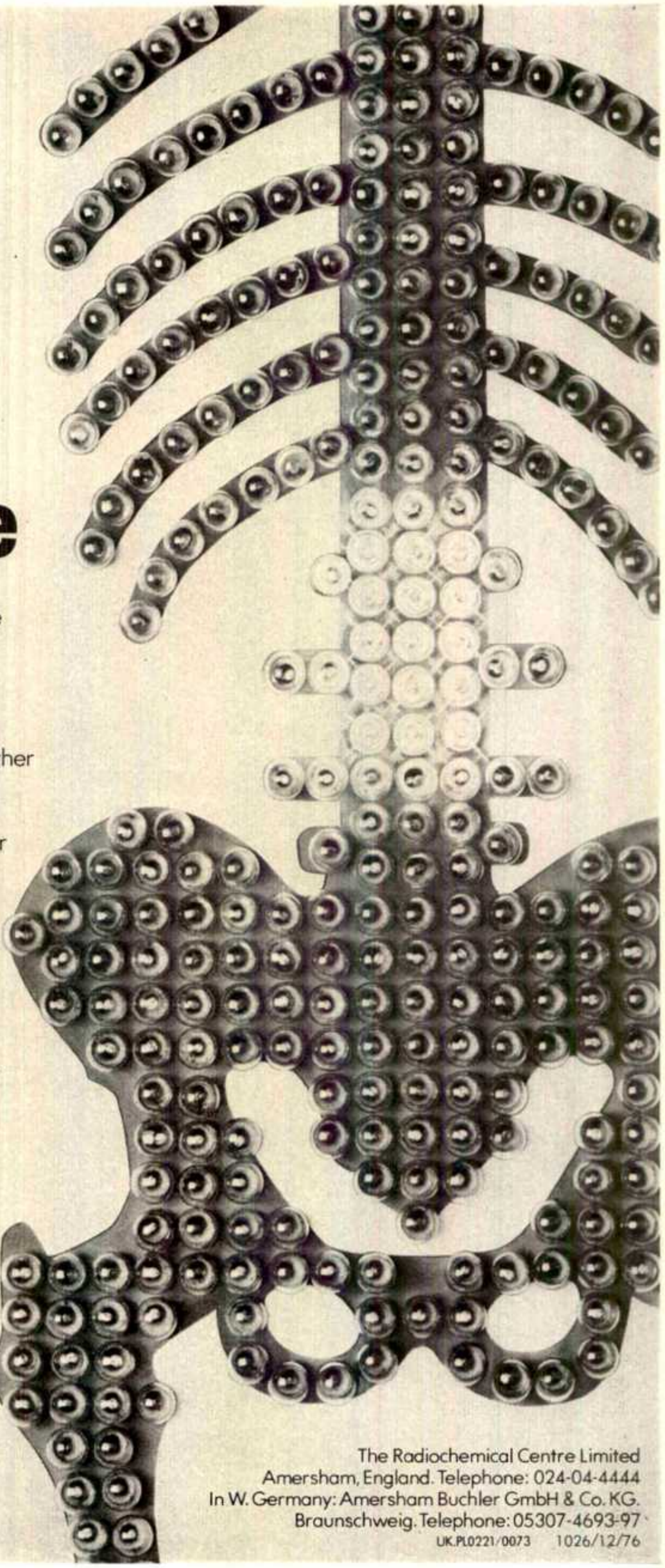

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(1) Subramanian *et al*, *J. Nuc. Medicine*, vol. 16, pp. 744-755, 1975.

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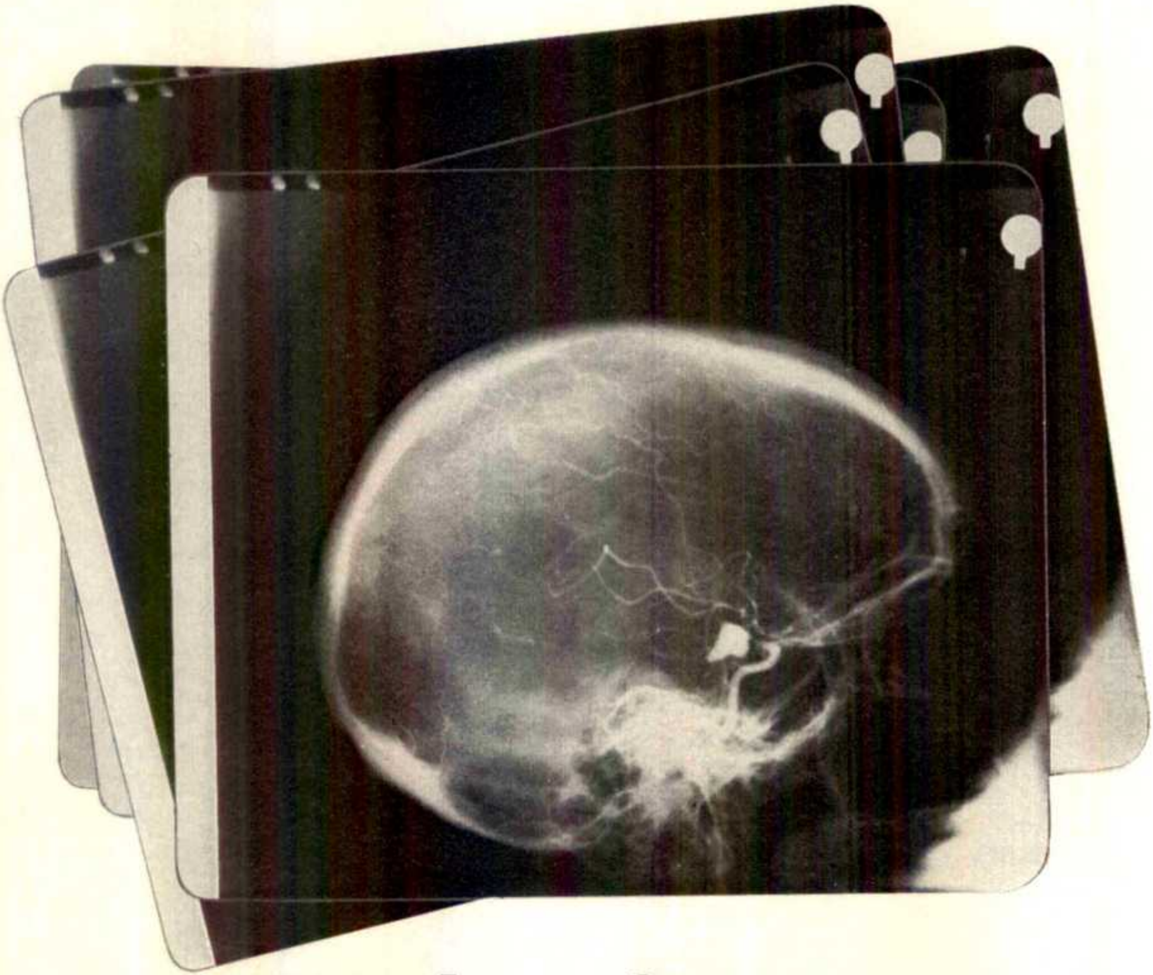

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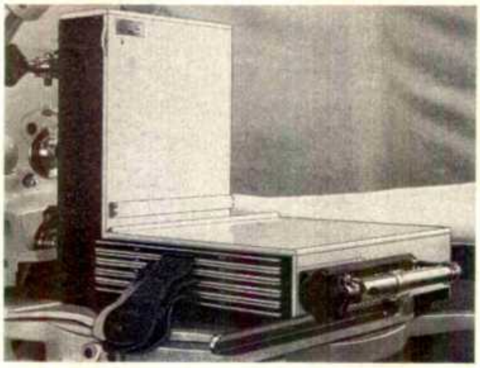

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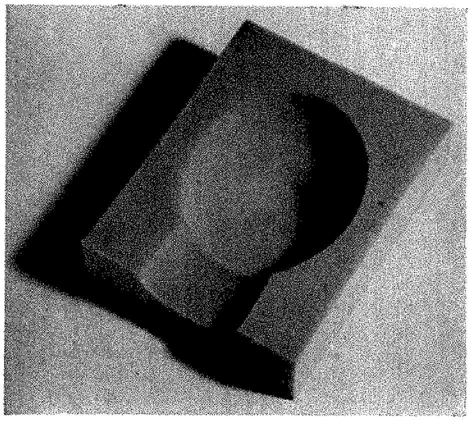

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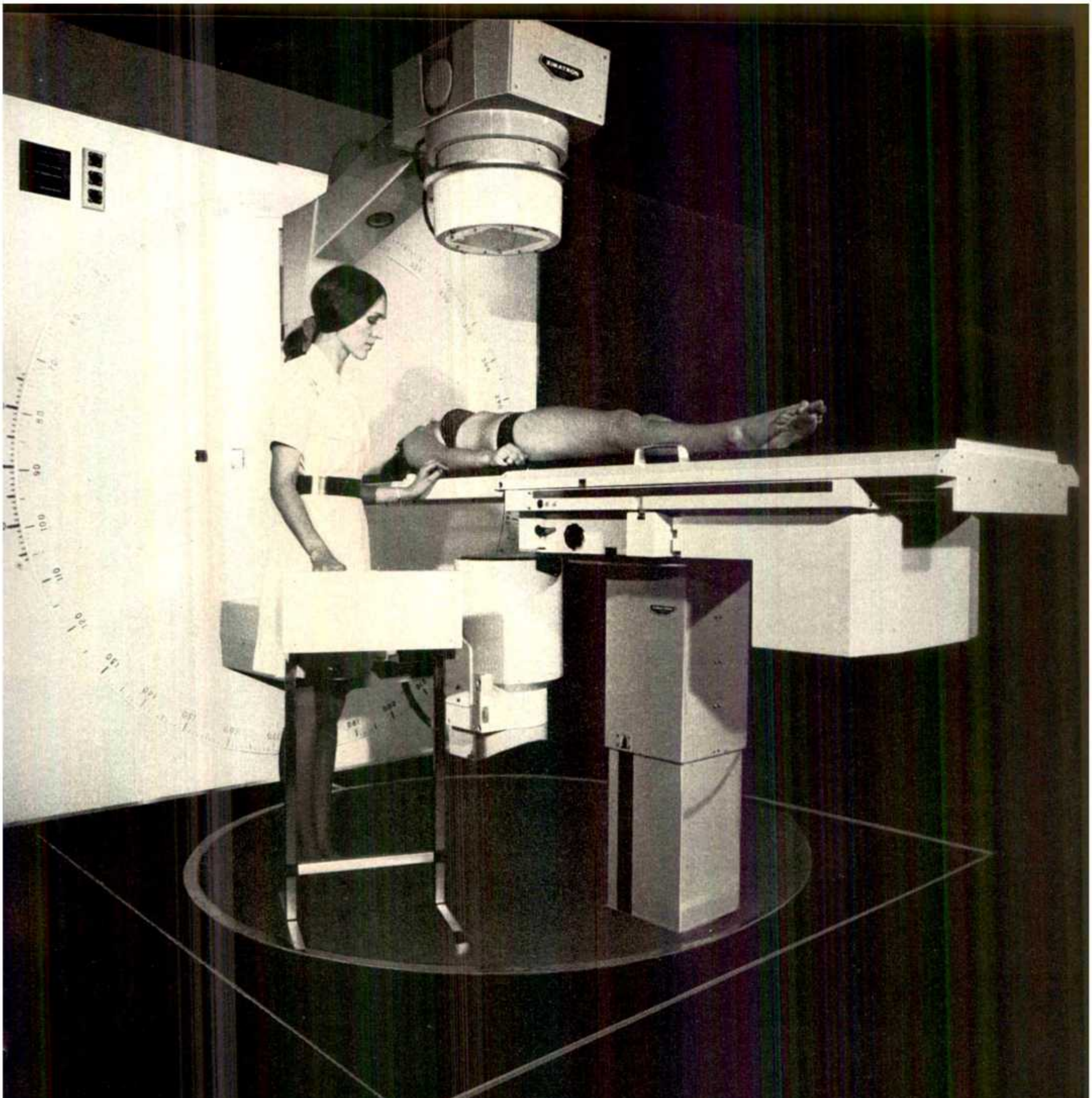

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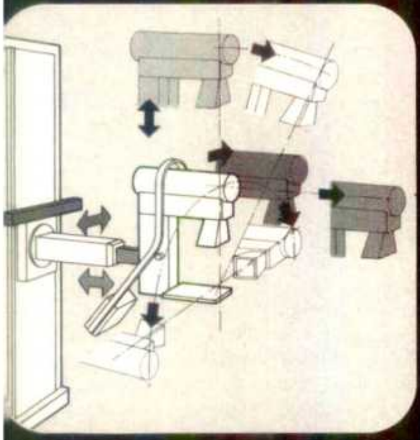

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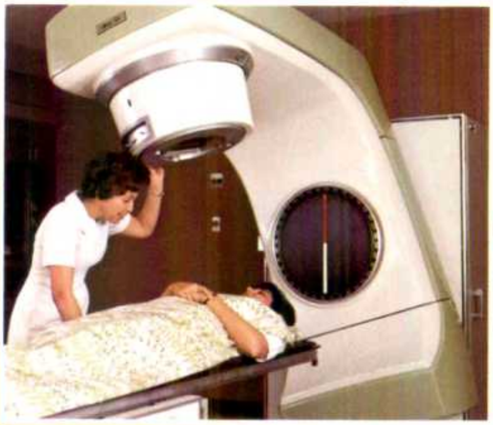

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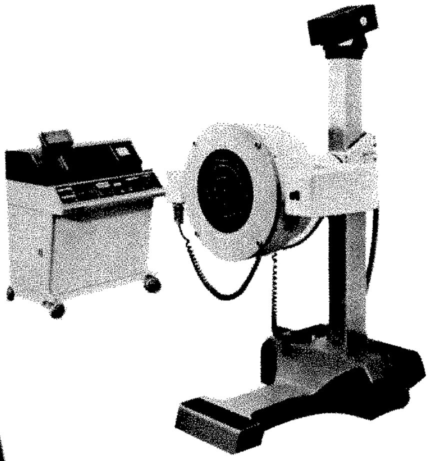

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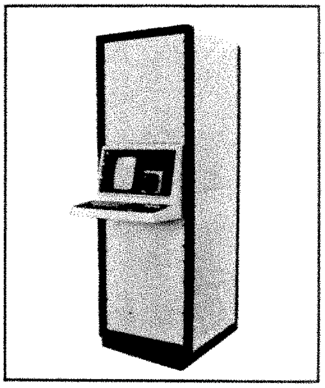

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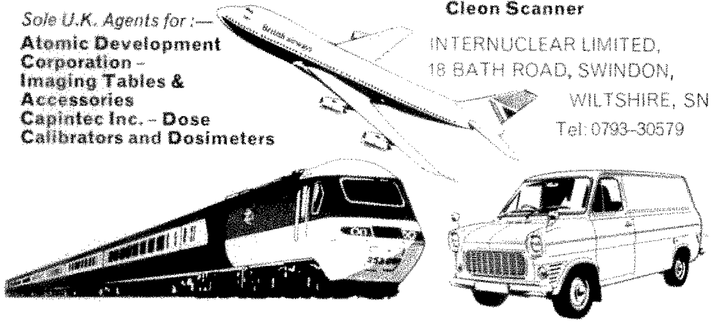

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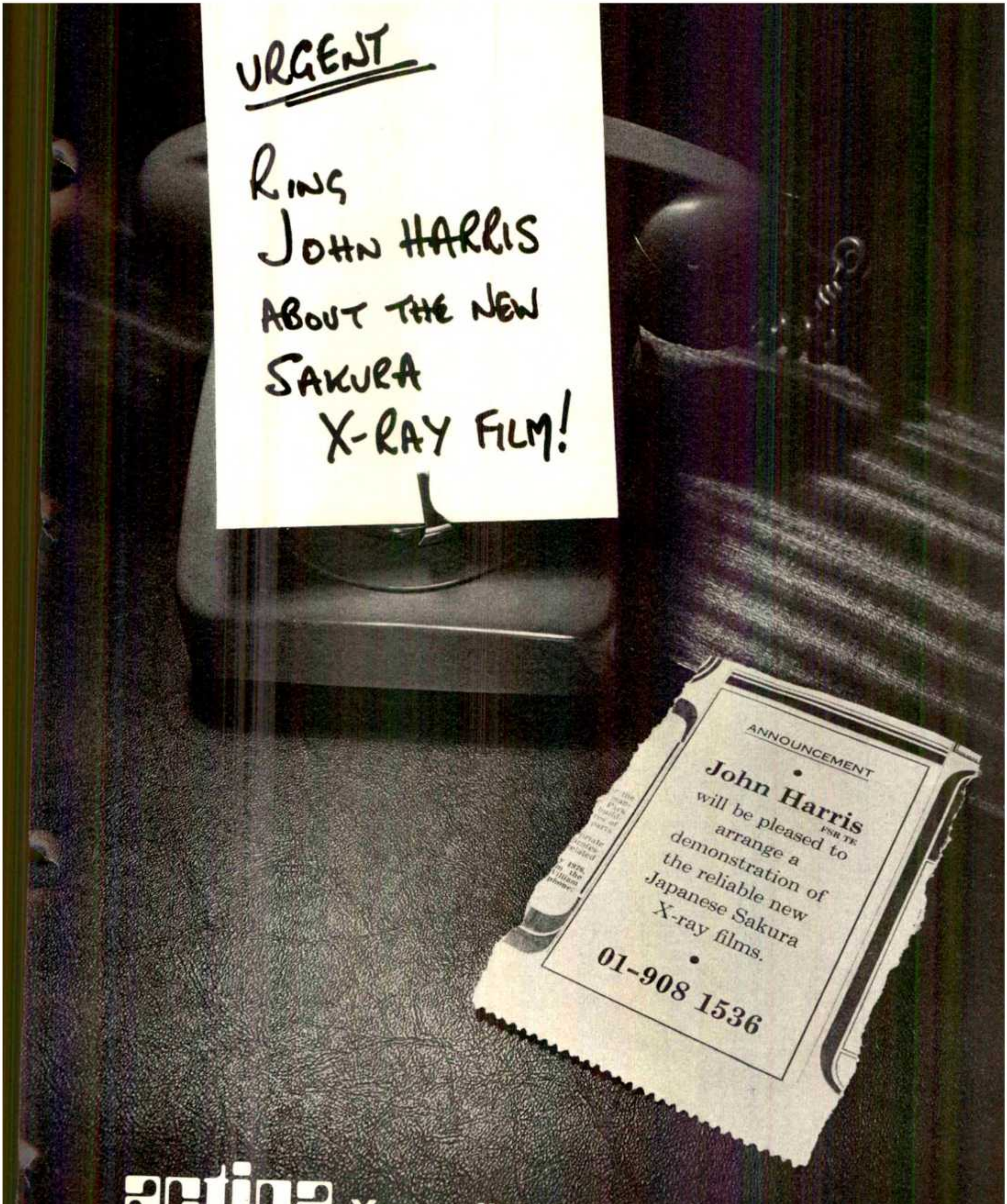

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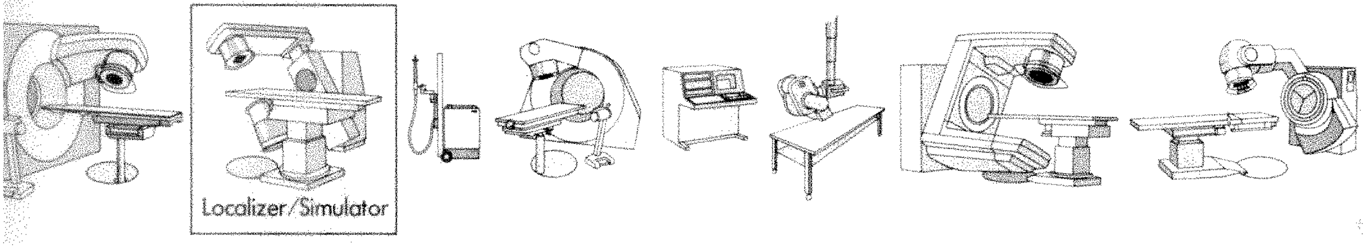

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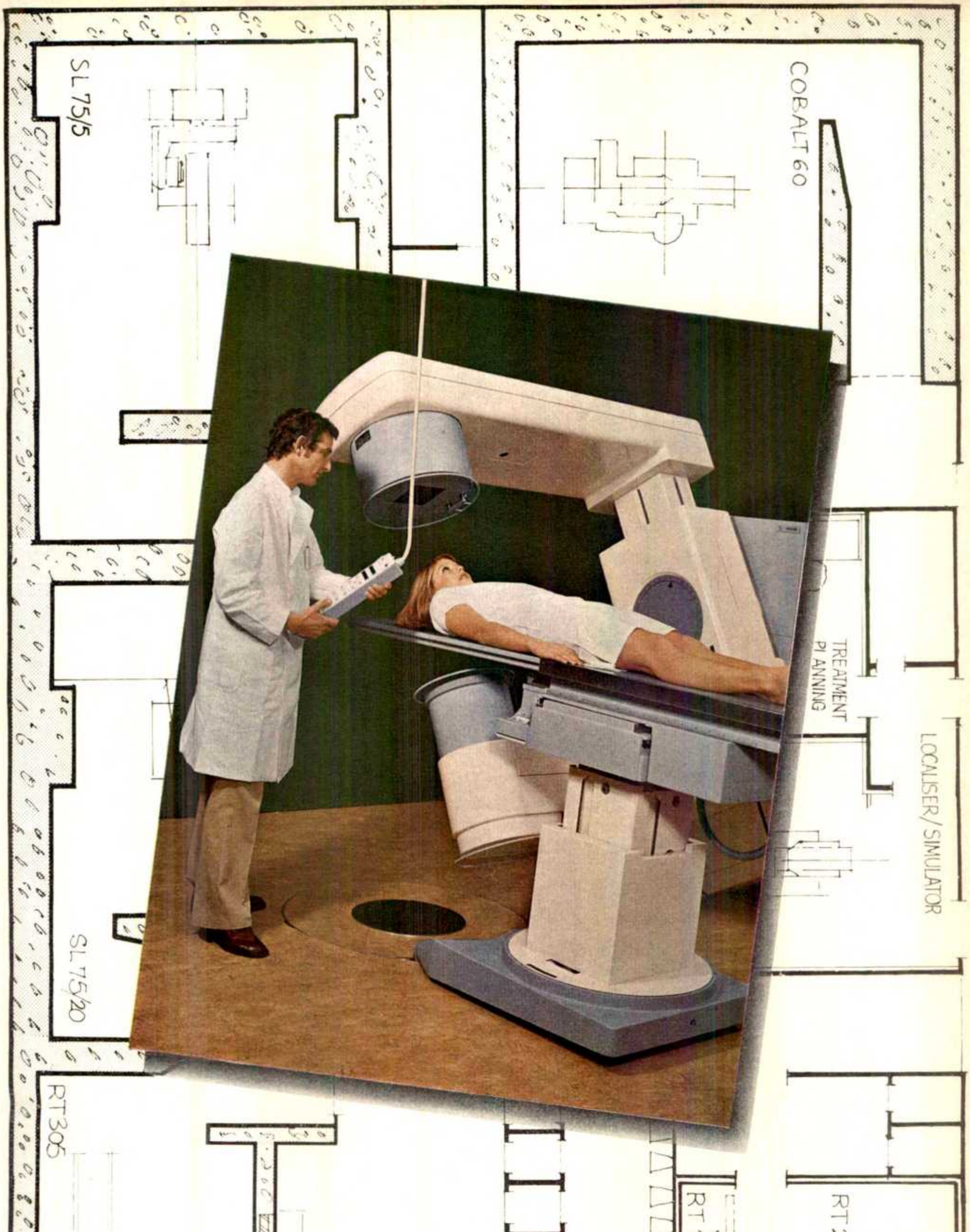

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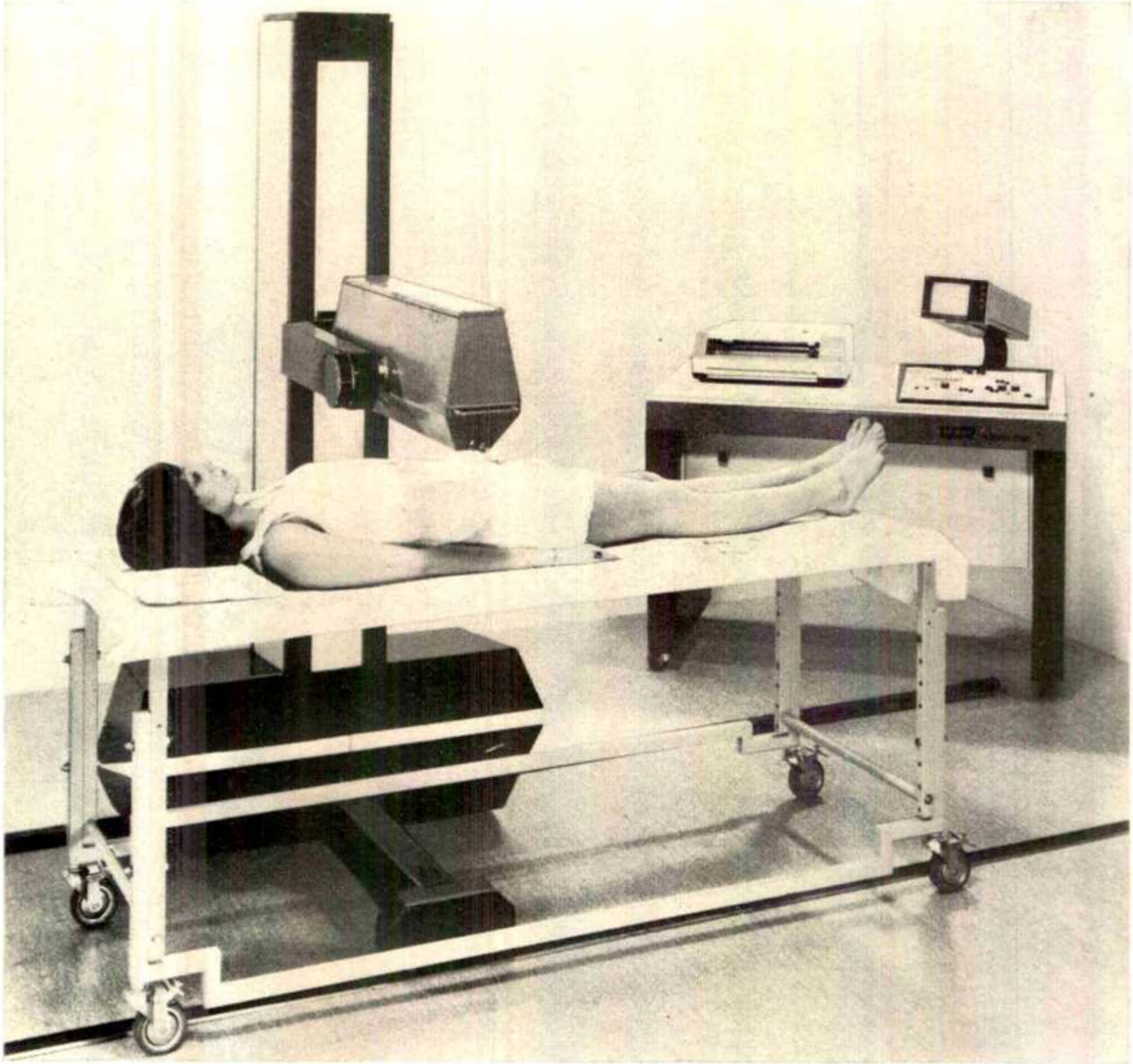

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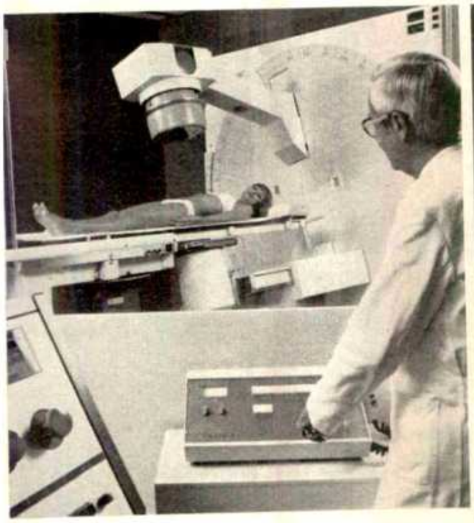

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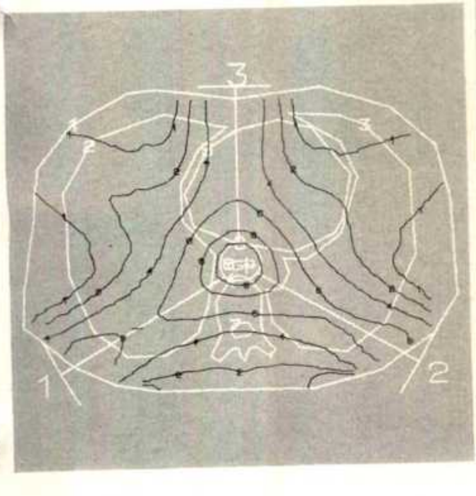

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It is by merest chance that our office premises at 5 High Street, Bushey Village (on which we have recently been served with a Preservation Order), are not included in the above famous picture, which was exhibited by Sir Hubert Herkomer in the Royal Academy in 1890. Had the view extended a few yards further to the artist's right our little building might have been recorded for posterity.

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The British Journal of Radiology

Radiology now

Therapeutic angiographic embolization*

The accepted term "Interventional radiology" (Wallace, 1976) is imprecise. It refers here to an increasing number of clinical situations where the diagnostic radiologist can offer, by means of the angiographic catheter, obliterative treatment that is sometimes temporary, but may be permanent. "Therapeutic angiographic embolization" is more appropriate.

Sites embolized and materials used read like a supermarket shopping list for a long week-end. Gastrointestinal haemorrhage in the poor risk surgical patient heads the list of sites. The left gastric or the gastroduodenal arteries can be obliterated to treat bleeding gastric or duodenal ulcers respectively. Once endoscopy has established the site of bleeding in the gut, embolization should be considered if the intravenous or intra-arterial vasoconstrictor therapy fails. It may represent the definitive treatment, or halt bleeding long enough to permit surgery. Selective embolization of the pancreatico-duodenal arteries has prolonged life in the patient with a sloughing, bleeding, inoperable carcinoid tumour of the duodenum. In portal hypertension, gastro-oesophageal collaterals can be selectively catheterized from the portal vein, then obliterated. Entrance to the portal vein is equally feasible by the transhepatic or transjugular routes. Unilateral renal disease, especially with haematuria, forms another large group. Ruptured kidney, A–V fistula (some following biopsy) and renal carcinoma are readily embolized. Intracerebral and spinal cord vascular malformations, and vascular tumours of the face with associated epistaxis have been obliterated, and bone tumours infarcted with radioactive emboli. Other indications are gynaecological malignancies and pelvic fractures. In the latter, a small arterial bleeder from the iliac system may be seen and can safely be embolized, on account of cross-vascularization in the healthy pelvis (Katzen *et al.*, 1976). In such a patient, with an immense associated haematoma, no surgeon would relish searching for a small arterial bleeder. Splenic artery emboli have been used to treat hypersplenism, and the hepatic artery embolized in primary and metastatic liver tumours.

Materials used range from the simplest—autologous blood clot or subcutaneous tissue—to mechanical devices made of wool, cotton, or stainless steel coils. Simple blood clot, even if modified with thrombin, has a short life (hours to days). Gelfoam powder or sponge is widely used, is intact at two weeks, and may be mixed with thrombin or sotradecol, the latter being used as an intimal sclerosant. It is important, however, to seek a chemical or a material that will be permanent. Isobutyl-2-cyanoacrylate (IBC), lead shot, or plastic microspheres (silastic) ought to lie in this category. Other methods include silicone rubber compounds, ferromagnetic silicone, balloon catheters, and transcatheter electrocoagulation.

When to embolize? The clinical situation, the imagination of the referring clinician, and the enthusiasm and skill of the angiographer are determining factors. Let "early rather than late" be the guiding rule. For example, early embolization in a patient with frank haematuria from a renal carcinoma stops blood loss at once and collapses tumour vessels. Goldstein *et al.* (1976) use this routinely 24–48 hours before surgery, which is simplified as a result of tumour shrinkage and a fitter patient. Unfortunately, the bleeding cirrhotic patient is often offered to the radiologist at a late stage of disease, suffering from liver cell failure, bleeding tendency, and gross ascites. He is unfit for surgery, and obliteration of bleeding gastro-oesophageal varices through a tiny hard liver is technically difficult. The better candidate is the young cirrhotic with fair liver function and one severe bleed. Obliteration of those varices which bleed and threaten life will divert portal venous blood to protected collaterals which are not easily traumatized. Whatever the stage of portal hypertension, the bleeding varices can be obliterated in 60% of patients (Scott *et al.*, 1976). The patient with hepatic malignancy will probably have well established disease when presented to the radiologist. Following hepatic artery embolization, the enormous liver shrinks and the patient feels more comfortable. Some improve remarkably (Pereiras, 1976), but a longer overall survival rate is unproven.

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What to use? The ideal agent should be radio-opaque, cause total obliteration of the artery or vein, and last for ever. Thrombin-induced clot recanalizes as may thrombus elsewhere in the body. 2×5 mm cubes of Gelfoam sponge soaked in contrast are the most universally used and last weeks or months. However, in one series four of 11 such patients bled again between four hours and 14 days (Goldman *et al.*, 1976). IBC has been shown to provide localized and permanent vessel occlusion (Dotter *et al.*, 1975), but may cause trouble with catheter withdrawal. Radio-opaque plastic or metal microspheres may be the definitive choice. As yet there is no follow-up in embolized patients beyond two years.

Complications? Necrosis of stomach, small bowel and gall-bladder are reported following embolization of their arteries. As the stomach has multiple sources of blood supply, left gastric artery occlusion rarely causes gastric infarction, but the surgically resected stomach is at risk, as is the atheromatous patient. In liver embolization, the catheter should be advanced beyond the cystic artery origin to avoid gall-bladder necrosis. Abscess formation has occurred after renal and splenic infarction, and in both these organs occlusion itself causes severe pain requiring opiates for up to 48 hours. Post-infarction fever is common, possibly due to tissue necrosis. Renal failure was precipitated in two patients with renal infarction. One of these died, and autopsy revealed tubular necrosis. The patient had received in excess of 300 ml contrast medium (Goldstein *et al.*, 1976). In a long procedure with multiple increments of contrast, it is essential not to exceed 1g iodine per kg body weight.

The lesson is clear. Perform these therapeutic procedures with extreme care—the artery closest to the site of bleeding or to the tumour should be subselectively catheterized. Undoubtedly the smaller the vessel to be occluded, the greater the likelihood of success and safety of the procedure (Goldman *et al.*, 1976). A coaxial system will facilitate catheterization of smaller vessels (Dotter *et al.*, 1972). There is no place for a cavalier attitude in performing therapeutic angiography. Catheter position must be constantly rechecked. The theory that if the coeliac trunk is catheterized, the embolus will, due to flow dynamics, find its way to the gastric extravasation site fed by the left gastric artery, is unproven.

Newer forms of body imaging, including ultrasound and computerized axial tomography, will diminish the number of angiograms requested for diagnosis. Though angiography is unrivalled in demonstrating the vascularity of a lesion, an actively bleeding ulcer, or a small vascular endocrine tumour, the future will surely see more therapeutic use of the angiogram. It is impressive that a mediastinal parathyroid adenoma causing hyperparathyroidism has been both identified and embolized (Doppman *et al.*, 1975). Nevertheless, most radiologists will be offered the bread under the caviar, and this will often be the patient with the gastrointestinal bleed. The outcome of a successful embolization is immediate and astonishing. Therapeutic embolization certainly deserves consideration in any patient whose angiogram shows active extravasation of contrast medium.

Robert Dick

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APRIL 1977

A comparison of radiography and radioisotope scanning in the detection of Paget's disease and in the assessment of response to human calcitonin

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ABSTRACT

In eight patients with symptomatic Paget's disease, radiographs and radioisotope bone scans have been compared before treatment by high dose synthetic human calcitonin (CIBA 47175-Ba) and three months and 12 months later. In six patients quantitative radioisotope scans allowed calculation of relative radioactivity in normal bone, Paget's disease and bone adjacent to osteoarthritic joints. Comparison of radiographs and scans showed 69 sites diagnosed as Paget's disease on both examinations; nine sites showed radiographic changes of Paget's disease but had negative radioisotope scans and two sites were abnormal on the scan but radiologically normal. One of these two reverted towards normal during treatment with calcitonin.

Comparison of analogue scans done at three months and 12 months with initial scans showed diminished uptake in Paget's disease compared with normal bone, and quantitation showed this was due to decreased absolute uptake in Paget's disease and a slight increase in normal bone. Osteoarthritic bone showed no significant response to calcitonin.

The diagnosis of Paget's disease, although originally based on clinical observation, now largely rests on its radiographic appearance. In most patients no biopsy is performed as the characteristic radiographic changes in bony architecture are taken as diagnostic proof.

A radioisotope bone scan can also be used to show areas of diseased bone. Increased accumulation of strontium 85, strontium 87m, fluorine 18 and technetium-labelled phosphate compounds is seen in abnormal bone (Bauer and Wendeberg, 1959; Bauer, 1968; Klein and Lund, 1964; Shirazi *et al.*, 1973; Miller *et al.*, 1974; Khairi *et al.*, 1973). The differential uptake of radionuclide into abnormal and normal bone allows comparative measurements to be made and can be used to follow the response of Paget's disease to treatment (Altman *et al.*, 1973; Serafini *et al.*, 1973; Russell and Lentle, 1974).

The present paper describes a prospective study comparing the radiographs and bone scans on eight patients with Paget's disease before treatment with a high dose (2.0 mg daily) of synthetic human calcitonin (CIBA 47175-Ba) and three months and 12 months after beginning treatment. The concentration of radioactivity in abnormal compared with normal bone was measured on each occasion and this sequential study was compared with clinical and biochemical response to therapy.

PATIENTS AND METHODS

Eight patients were studied, all with radiological evidence of Paget's disease at one or more sites associated with bone pain (*see* Table I). An initial radiographic survey and whole-body radioisotopic scan were performed, the patients then starting treatment with 2 mg synthetic human calcitonin intramuscularly per day. Further examination of the skeleton was performed at three and 12 months.

Radiology

Radiography was done in the Academic X-ray Unit using standardized factors, film and positioning in order to achieve reproduceability (Doyle *et al.*, 1974). The radiographs were examined by one author (FHD) without knowledge of the scans, and the results recorded on skeletal charts. Abnormalities were recorded as "Paget's Disease" and also "Degenerative Arthritis". No grading of "severity" of either type of lesion was used but its exact extent was charted.

Quantitative radioisotope scanning

Whole-body radioisotope scanning was performed four hours after the intravenous injection of 10 mCi technetium-labelled ethane-1-hydroxy-1,1-diphosphonate ($^{99}Tc^{m}$ EHDP). Freeze dried kits supplied by Duphar Laboratories were used to prepare the labelled compound, the injections for the first two scans on all patients being made from the same batch of kits, and those for the third scan being

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TABLE I

Biochemical and clinical information on the six patients in whom sequential quantitative scanning data are available

			Biochemistry Serum alkaline phosphatase I.u/l			Urine hydroxyproline mg/24 h			Clinical assessment	
Patient	Sex	Age (yrs)	0	3 mo.	12 mo.	0	3 mo.	12 mo.	Initial	Follow-up
G.B.	M	62	1310	475	635	237	104	140	Pain neck, low back, hips and femora. Tenderness L3–L5. Left lower leg shortened by 2 cm.	No change in back or hip pain. Improvement in neck and femoral pain at 3 mo. Slight persisting lumbar tenderness at 12 mo.
V.B.	F	56	93	65	55	31	35	N.D.	Pain left knee, ankle and posterior surface left tibia. Tenderness and warmth left knee. No deformity.	Pain improved in left knee at 3 mo. with no change in pain tibia and ankle, slight tenderness and warmth left knee. No tenderness or warmth left knee at 12 mo., persisting pain left ankle.
L.B.	M	66	1210	1050	1238	169	113	128	Frontal headaches, deafness on right. Gross frontal bony overgrowth, skull warm.	Headaches "occasional" at 3 mo and "rare" at 12 mo. No change in deafness. Skull temperature decreased at 3 mo.
G.M.	F	60	526	320	286	164	133	N.D.	Frontal headaches, pain tibiae and pelvis. Tenderness right tibia. Deformity and warmth right tibia, skull warm.	Headaches improved at 3 mo. pain tibiae improved at 12 mo., with persisting/ pain in pelvis. Warmth and tenderness right tibia, improved at 3 mo. and absent at 12 mo. Some decrease in skull temperature at 3 mo. and marked improvement at 12 mo.
I.S.	F	65	820	269	256	101	104	N.D.	Pain low back and slight discomfort across shoulders. Increased lumbar lordosis with scoliosis to right. Left leg shortened by 3 cm.	Marked improvement in back pain some improvement shoulder pain at 3 mo. Improvement maintained at 12 mo.
R.S.	M	64	807	177	106	151	64	49	Pain both knees, right tibia and low back. Deformity and warmth right tibia.	Improvement in pain back and right knee at 3 mo. with persisting pain left knee, improvement in all areas at 12 mo. Tibial warmth absent by 3 mo.

Serial alkaline phosphatase and urinary total hydroxyproline were measured by automated techniques and the mean of three daily measurements is given. The normal range for alkaline phosphatase is 30–130 I.u/l and the upper limit of normal for urinary hydroxyproline is 45 mg per 24 hours.
N.D. = Not done.

made from a second batch. A standard preparation procedure was used so that all injections contained the same quantity of radioactivity and weight of EHDP, and were administered at the same time after preparation. A test of the preparation using descending paper chromatography showed that 90% of ^{99}Tc^{m} was bound to EHDP. Scanning was performed using a double-headed rectilinear scanner whose analysers were set to detect radiation between 127 keV and 162 keV. Data were recorded on paper tape for subsequent processing by computer, using the principle outlined by Williams *et al.* (1975). Additional data required were obtained by measuring the response of the detectors to the net injected radioactivity and by measuring body thickness using outlines taken in the scanning position. Data processing allows the calculation of the relative concentration of radioactivity in chosen regions of

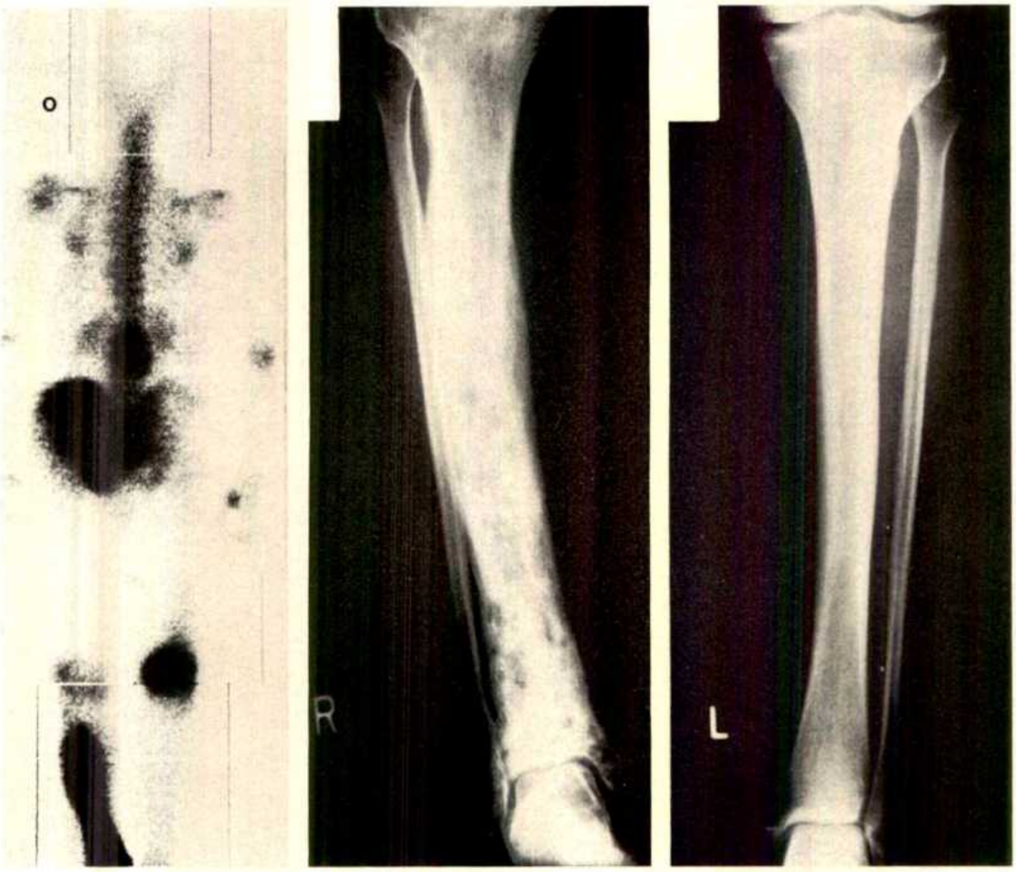

FIG. 1.

Radioisotope scan (left) and radiographs of right and left tibiae. The right tibia (centre) shows Paget's disease with gross disorganization of bony architecture corresponding to the bone scan. The left tibia also shows Paget's disease in the centre and upper shaft with osteolytic clefts and loss of cortical margins. The bone scan of the left tibia appears normal.

the scan. Where possible, two areas of normal bone, two areas of Paget's diseased bone and one osteoarthritic joint were chosen, and the ratios of concentrations in the regions of abnormal bone to those in the regions of normal bone were calculated. The same portions of the skeleton were used on sequential scans. Correction for radioactivity in soft tissue was not made since only relative concentrations in the same patient were to be compared.

Assessment of the analogue scans was done by one author (J.P.L.) and recorded on skeletal charts. These were subsequently compared with the radiographic charts.

RESULTS

Comparison of radiography and radioisotope scans

(a) *Paget's disease*

TABLE II

COMPARISON OF 80 BONY SITES DIAGNOSED AS PAGET'S DISEASE ON RADIOGRAPHS OR RADIOISOTOPE SCANS

Radiograph Scan	Positive Positive	69
Radiograph Scan	Positive Negative	9
Radiograph Scan	Negative Positive	2

Correlations of the two skeletal images for eight patients are given in Table II. Sixty-nine sites involving a bone or part of a bone showed abnormalities which were diagnosed as Paget's disease on both examinations. Nine sites were diagnosed by radiography as involved with Paget's disease but not so diagnosed on the radioisotope scan (*see* Fig. 1).

Two sites showed clear abnormalities on the scan, but no radiographic changes were discovered even on careful review (*see* Fig. 2).

(b) *Osteoarthritis*

A number of joint areas showed increased activity on the scans interpreted as being due to degenerative arthritis. Comparison of these areas with radiographs confirmed the presence of joint narrowing and osteophytes. However, other joints were noted on the radiographic charts as showing evidence of osteoarthritis which were not reflected in the scans.

Sequential radioisotope scans

(a) *Paget's disease*

When the analogue skeletal scans done at three months and 12 months after beginning calcitonin treatment were compared with the initial scans, diminution of uptake in Paget's bone compared with that in normal bone was visible (*see* Fig. 3). Quantitation of these changes was available in six of the patients and is shown in Fig. 4. It is seen that the ratio of the radioactivity in Paget's bone to that in a normal reference bone decreased in all patients. In patients where two areas of Paget's disease were examined, the changes in ratio were roughly parallel (*see* Fig. 5). The decreased ratio was mainly due to decreased absolute uptake in abnormal bone, but also to increased absolute uptake in normal bone.

Of the two sites which were scan positive but radiographically negative, only one could be com-

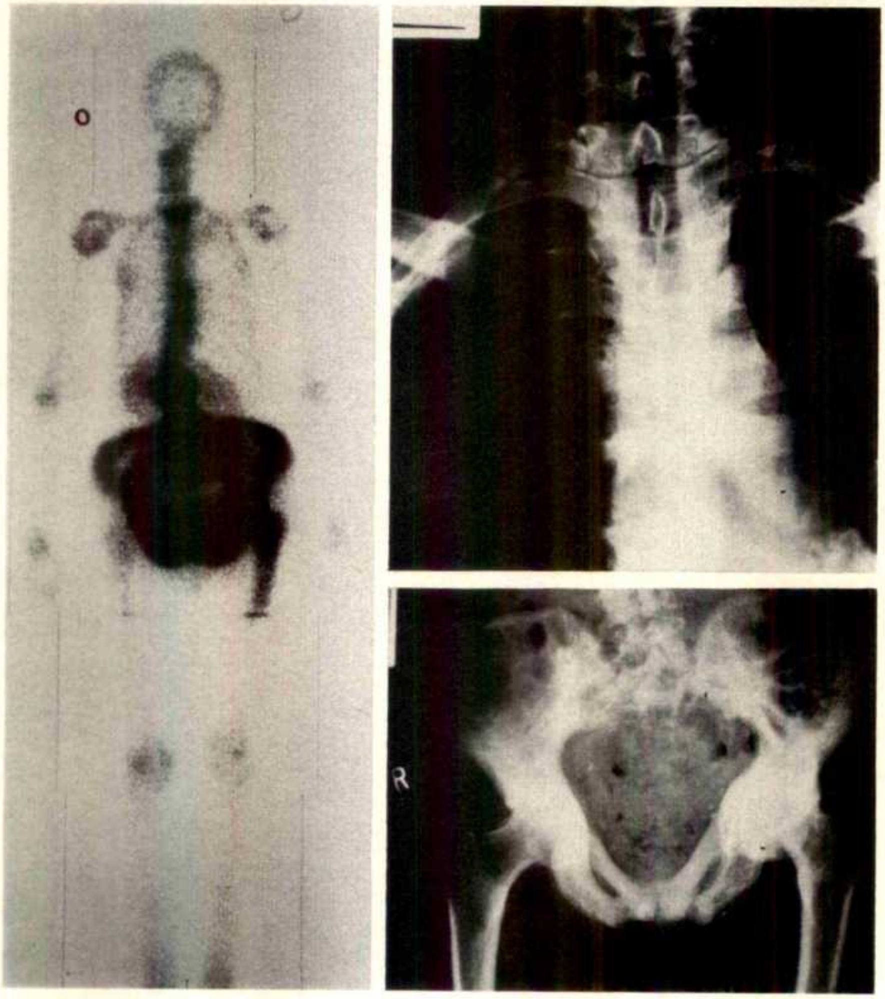

FIG. 2.

Radioisotope scan showing marked increase of radioactivity in pelvis, left femur and lumbar spine. These areas showed Paget's disease radiologically (*see* pelvis, lower right). There is also increased activity in D2 vertebral body which appears normal radiologically. This area reverted towards normal on sequential scans.

pared on sequential scans and this showed decrease in relative uptake of radioactivity during calcitonin therapy.

(b) *Normal and osteoarthritic bone*

Where two areas of normal bone could be outlined on sequential scans, the ratios of the uptakes in the two regions were very similar in all three scans.

The scans of three patients with osteoarthritic bone showed only slight changes in abnormal to normal ratios under calcitonin (*see* Fig. 6). The behaviour of osteoarthritic bone is therefore in marked contrast to that of Paget's bone.

Sequential radiological changes

Radiological changes were observed in only one patient over the 12 month period. Two resorption fronts at the upper level of the Paget's disease in the right tibia disappeared and became consolidated with new bone. This bone showed a marked reduction in uptake of labelled diphosphonate over the same period. The two areas of bone which were scan positive, X-ray negative at the start of the study were still X-ray negative after 12 months.

DISCUSSION

The diagnosis of Paget's disease in the absence of bone histology usually depends on the characteristic changes seen in skeletal radiographs. Thus, the presence of appositional new bone on periosteal surfaces resulting in a widening of the bone, the appearance of resorption clefts or more extensive lytic areas in the cortex, and the disorganization of the normal trabecular pattern on the endosteal surfaces typify Paget's disease radiographically. The natural history of these changes, however, is

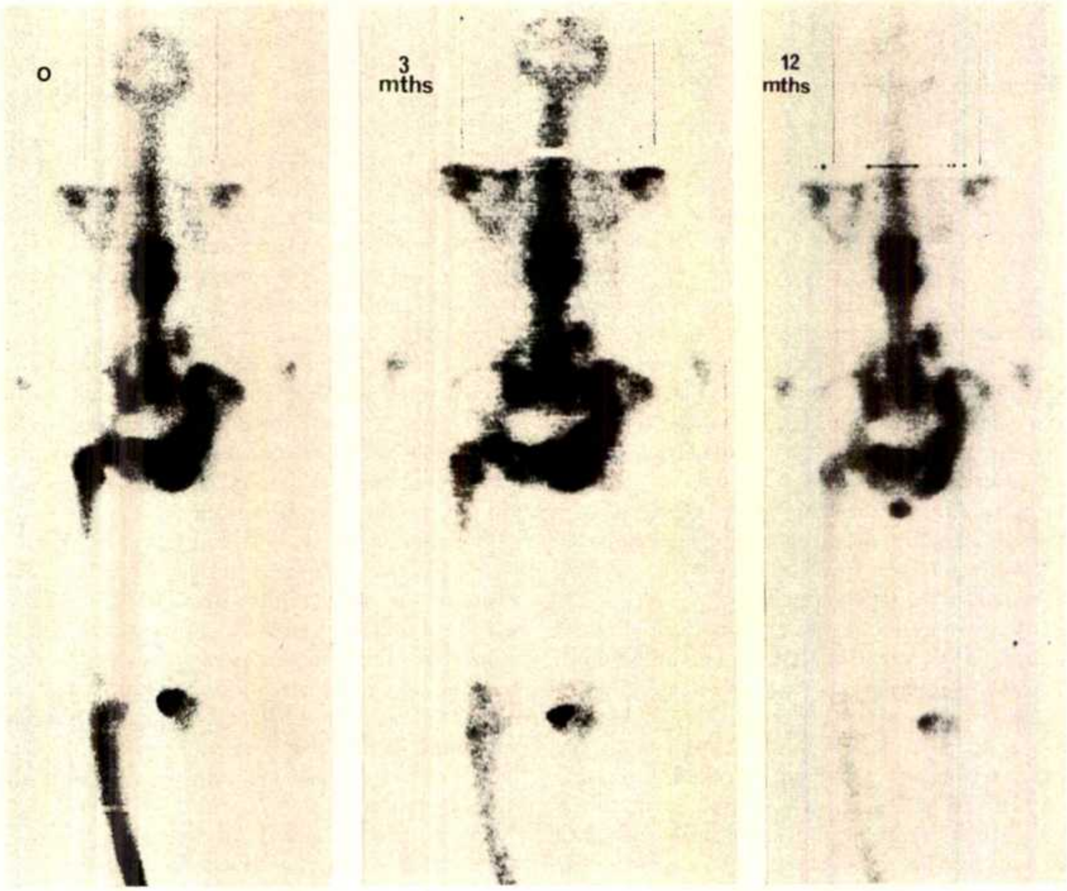

FIG. 3.

Sequential radioisotope bone scans prior to (0), at three months and at 12 months after starting treatment with synthetic human calcitonin showing diminution in the relative uptake in Paget's disease compared with normal bone.

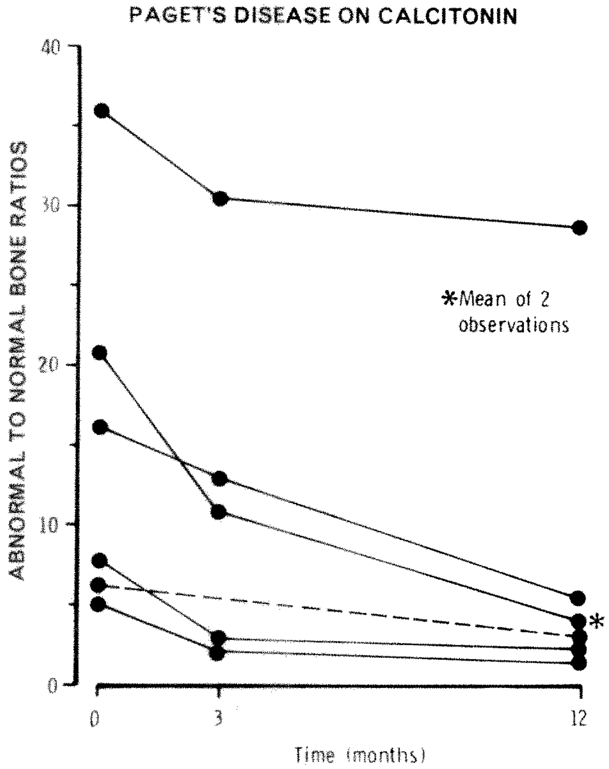

Fig. 4.

Graph showing ratio of concentration of radioactivity in Paget's disease compared with normal bone in six patients under treatment with human calcitonin.

unknown and it cannot be clearly stated what comprises an "early" lesion or whether such changes might revert to normal bone as a part of their natural cycle. It is true to say, however, that such radiographic changes reflect past and not necessarily present disease activity.

The correlation of radiographic changes with radioisotope scans has been recorded by a number of authors. Shirazi *et al.* (1973) showed in 80 patients a close correlation between radiographs and scans and this was also noted by Miller *et al.* (1974), but in both instances the results of the radioisotope scans were incidental findings and not prospective investigations. A prospective study was reported by Khairi *et al.* (1973), using fluorine 18 bone scanning in a carefully studied group of 22 patients. In this group a total of 64 lesions was detected but it was noted that 15 lesions were only visible on the scan and 13 only on the radiographs. Of interest, these authors noted that 11 of the lesions not seen on the radiographs were symptomatic whereas none of the lesions seen only on the radiographs was associated with bone pain. The lesions only shown radiographically had a sclerotic appearance.

Our own findings, like those of Khairi *et al.* (1973), show that the lesions in Paget's disease fall into three groups. They are either detected both on the radiograph and on the scan (termed radiograph positive scan positive), on the radiograph alone (radiograph positive scan negative), or on the scan alone (radiograph negative scan positive). In the present study a total of 11 sites showed a disparity between radiographs and scans. Two sites showed a marked increase in uptake of radionuclide but appeared radiographically normal; one of these areas was seen to regress towards normal during calcitonin treatment and therefore by inference is Paget's disease. Nine sites showed radiographic changes with either little or no change visible on the radioisotope scan. It is tempting to suggest that the scan-positive, radiograph-negative sites reflect the disease process at an early stage when an increase in bone metabolic turnover may precede any architectural change. Obviously the truth of this surmise can only be ascertained by a follow-up study in this group of patients.

Radioisotope bone scans may also be used to study response to treatment in Paget's disease. Altman *et al.* (1973) used fluorine 18 and strontium 87m scans to study a group of 50 patients being treated with diphosphonates. They showed a qualitative improvement in 16 out of 28 patients on a high dose regimen with no change in 16 patients on a low dose regimen or placebo. A method of quantitation to be used in bone scans was described by Serafini *et al.* (1973), but the technique was limited to use over a small field (10 in. in diameter).

Treatment with synthetic human calcitonin has previously been associated with histological improvement in Paget's disease as shown by a reduction in the number of osteoclasts and the deposition of normal lamellar bone endosteally (Woodhouse *et al.*, 1971). Changes in bony architecture have also been noted radiographically. These have been recorded after 14 months calcitonin treatment (Doyle *et al.*, 1974) and in this present study changes were seen in one bone after 12 months. Biochemically, serial alkaline phosphatase and urinary total hydroxyproline often show a rapid response to calcitonin treatment but these are non-specific indicators of disease activity.

In the present study all sites of Paget's disease seen on the scans showed a reversion towards normal, *i.e.* a decrease in the radionuclide uptake during calcitonin treatment, although the response varied quite widely. The number of bones studied is insufficient to permit conclusions to be drawn

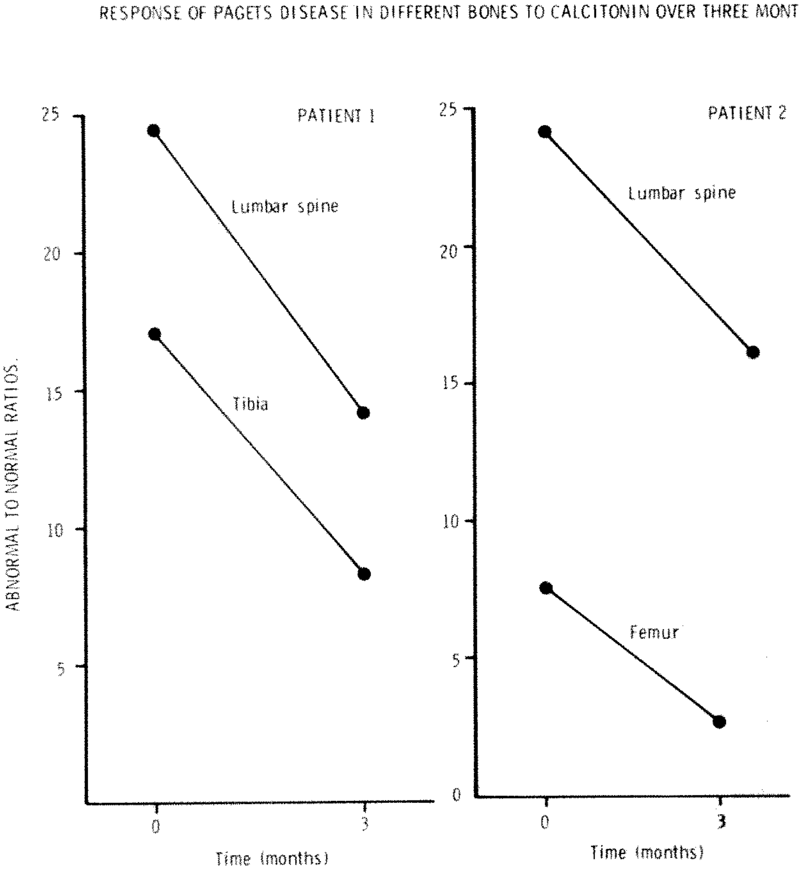

FIG. 5.
Graph showing response of two areas of Paget's disease to calcitonin during three months' treatment.

with respect to the response in relation to site or radiographic appearance. In general there is a correlation between the scan response and the biochemical response although in two patients (V.B. and I.S.) the decrease in radionuclide uptake correlated with a fall in alkaline phosphatase alone, the hydroxyproline changing very little, and in a fourth patient (L.B.) the scan response correlated with a fall in hydroxyproline while the alkaline phosphatase remained virtually unchanged. All the patients in this study showed a clinical improvement during calcitonin therapy.

Of additional interest is the difference in the scan response shown by Paget's and osteoarthritic bones. Calcitonin can be shown to counteract the resorption by osteoclasts when these are active as, for example, under the influence of parathyroid hormone (Aliapoulios *et al.*, 1966), whereas normal bone is unaffected. The difference in response

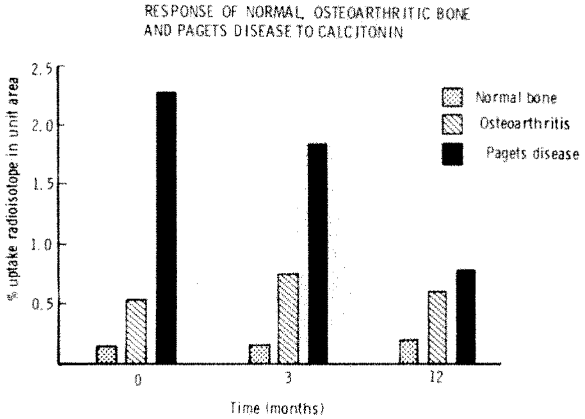

FIG. 6.
Histogram showing uptake of radioisotope in one patient in normal, osteoarthritic bone and Paget's disease expressed as a percentage of the injected dose recorded in a standardized area. The values are plotted before, at three and at 12 months after starting treatment with calcitonin.

between these two forms of abnormal bone, therefore, may reflect the level of osteoblastic activity.

This study clearly shows that quantitative whole-body scanning is a useful technique both in the diagnosis of Paget's disease and in following the response to treatment. It would appear that a combination of bone scanning and radiography will demonstrate a spectrum of disease which is wider than with either technique used alone and may represent differing phases of the underlying pathological process. If follow-up studies demonstrate that the scan positive radiograph negative areas represent early Paget's lesions it may well be possible to initiate treatment in appropriate cases at an earlier stage in the disease. In addition, in those patients who demonstrate apparent biochemical resistance to chronic treatment in the face of maintained clinical improvement, bone scans may help to differentiate between continued disease activity and a healing response of normal bone cells.

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The use of prostaglandin F2 alpha in selective visceral angiography

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ABSTRACT

Prostaglandin F2 Alpha has been used in 33 superior mesenteric and ten splenic angiographic studies. In each instance, improved anatomic detail was obtained after injection of the Prostaglandin. Unlike other vasodilating drugs, the use of Prostaglandin F2 Alpha improved the arterial as well as the venous phase of each study. No systemic haemodynamic changes or significant side effects were observed after injecting the drug, and it appears that Prostaglandin F2 Alpha is an ideal choice as a pharmacologic aid in angiography.

The angiographic demonstration of the venous circulation within the abdomen is important not only for the investigation of portal hypertension, but also in the pre-operative assessment of carcinoma of the pancreas and other malignant neoplasms (Buranasiri and Baum, 1972). Superior mesenteric and splenic angiographic studies often result in poor opacification of the venous phase of the study unless a vasodilating drug is first injected intra-arterially. Tolozoline and Bradykinin have been widely used to enhance opacification of the venous circulation, but these drugs may produce unwanted systemic haemodynamic side effects, and usually impair the quality of the arterial phase of the study (Davis *et al.*, 1975). We have been using another substance with vasodilating properties, Prostaglandin F2 Alpha, in abdominal angiography, in an attempt to

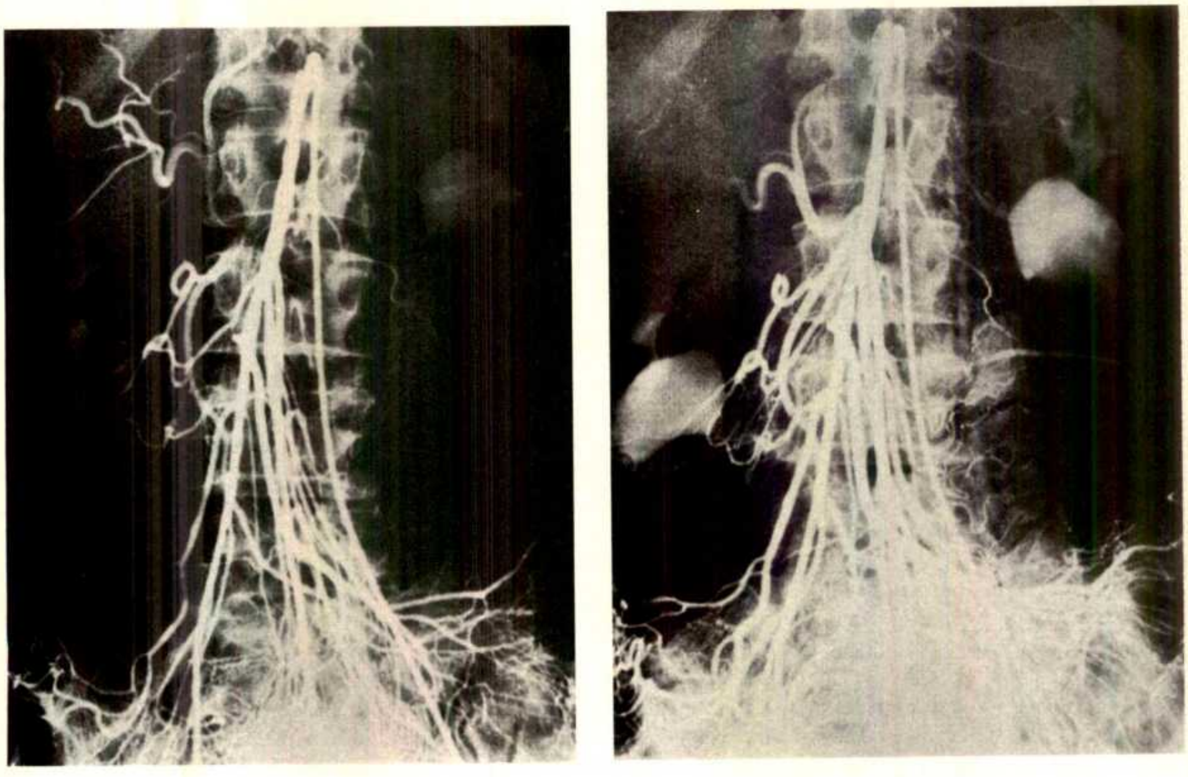

FIG. 1.

Superior mesenteric angiography in 63-year-old female investigated for suspected mesenteric ischemia.

(A) Control study, arterial phase.

(B) After the intra-arterial injection of Prostaglandin F2 Alpha: there is an increase in the size of all vessels, with dense opacification of the smaller vessels in the wall of the small bowel.

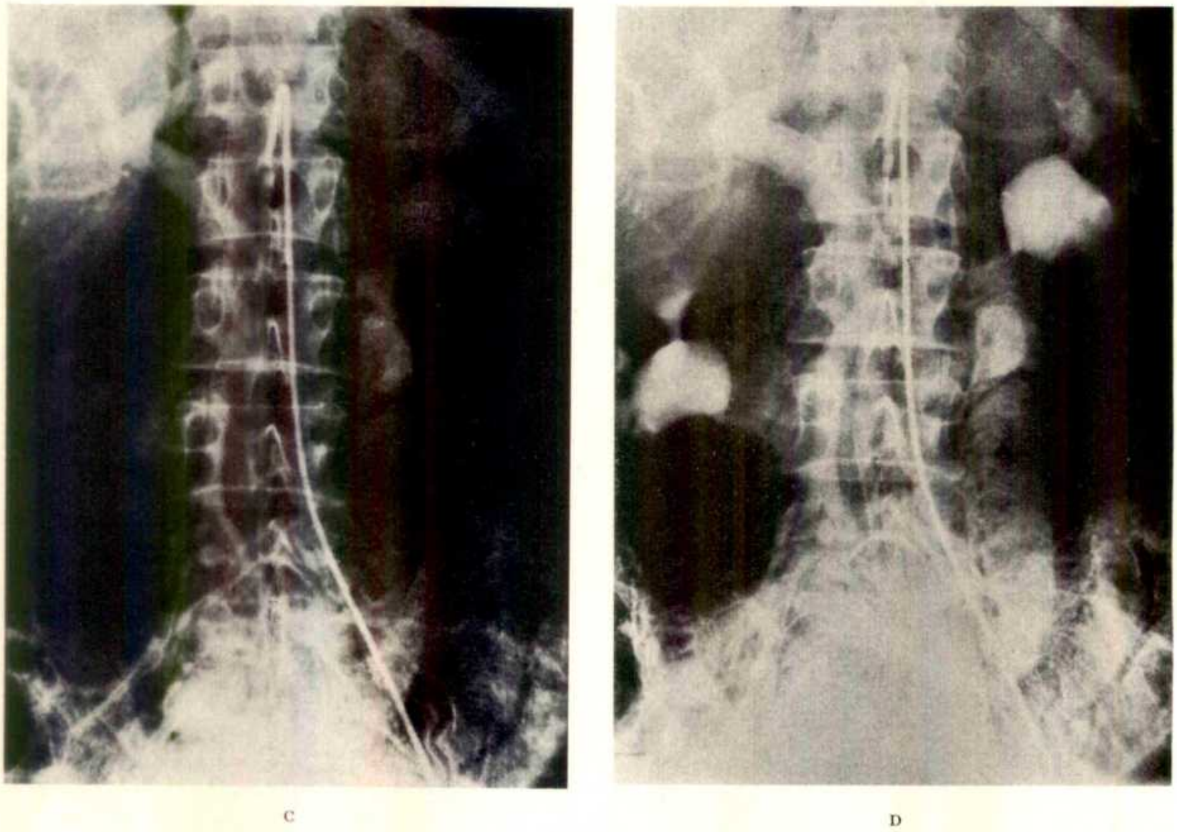

FIG. 1.

(C) Control study, venous phase.

(D) After Prostaglandin: the superior mesenteric and portal veins are increased in diameter, and more densely opacified; the wall of the small bowel is also more densely opacified.

improve anatomic detail. This paper describes the angiographic changes observed following the injection of this drug into the superior mesenteric and splenic circulation.

MATERIAL AND METHOD

Between April, 1975 and August 1976, Prostaglandin F2 Alpha was used during 33 superior mesenteric studies; in ten of these cases, selective splenic injections were also made. Fifty millilitres of Hypaque 65% were injected into the superior mesenteric artery, or 40 ml into the splenic artery, both before and immediately after the intra-arterial injection of Prostaglandin F2 Alpha. A pressure of 3 kg/cm^2 was used for the injections of the contrast medium. Eighty micrograms of the Prostaglandin were used for the superior mesenteric injection, and 60 micrograms for the splenic injection.

Twenty cases were referred for angiography of the pancreas for the evaluation of known or suspected pancreatic disease, five were referred for investigation of possible gastrointestinal neoplasm, and four for the investigation of suspected portal hypertension. Two patients were evaluated for blunt abdominal trauma, one for chronic gastrointestinal bleeding, and one for mesenteric ischaemia.

RESULTS

Superior mesenteric studies

Following the injection of Prostaglandin F2 Alpha, there was a measurable increase in the diameter of the superior mesenteric artery and its branches, compared with the control study. The superior mesenteric and portal veins were likewise increased in diameter, and more densely opacified (Fig. 1). In addition, the smaller arterial branches supplying the wall of the bowel were shown in detail, as were the small veins draining the bowel (Fig. 2).

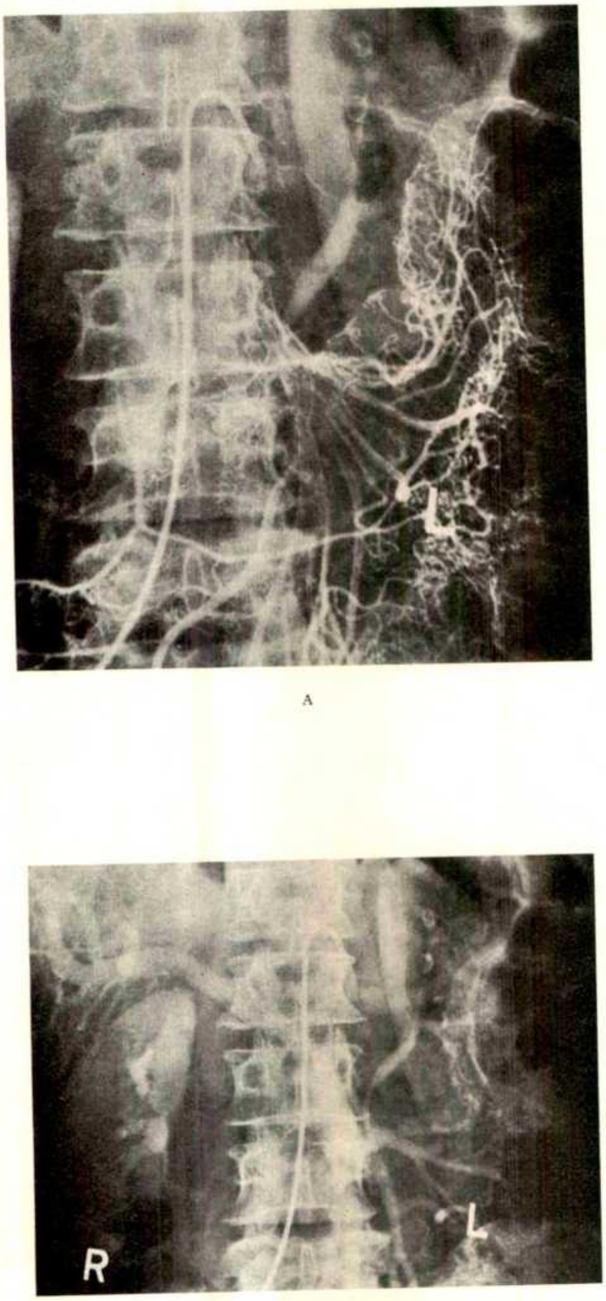

FIG. 2.

Superior mesenteric angiography in 50-year-old male investigated for recurrent gastrointestinal bleeding.

(A) Late arterial phase, after injection of Prostaglandin: the small vessels supplying the wall of the bowel are shown in detail.

(B) Venous phase: there is dense opacification of the small veins draining the wall of the bowel, and these are of the same density as the adjacent ureter. The mesenteric and portal vein, including the intrahepatic radicles are well opacified.

Splenic studies

After injection of Prostaglandin into the splenic artery, the splenic branches supplying the pancreas were significantly better filled than on the control study and this gave improved opacification of the body and tail of the pancreas. In half the cases, the pancreatic duct was easily identified, as was the lobular outline of the pancreas. The density of the splenic vein was increased in all instances, as was its size (Fig. 3).

No side effects were noted after the injection of Prostaglandin and there was no significant change in the blood pressure or heart rate.

COMMENT

The Prostaglandins are a group of biologically-active fatty acids which have the property of relaxing vascular smooth muscle. When injected intra-arterially, they produce local vasodilitation (Denker *et al.*, 1975). Davis *et al.* (1975) studied the effect of Prostaglandin E1 on superior mesenteric angiographic studies in 19 dogs, and found a 100% increase in the superior mesenteric arterial blood flow and consequently improved opacification of the portal venous system. The Prostaglandin injections resulted in no systemic haemodynamic changes. Denker *et al.* (1975) used Prostaglandin F2 Alpha in ten superior mesenteric angiographic studies in man and showed improved opacification of the venous anatomy, similar to that produced by Bradykinin. Evaluation of the superior mesenteric blood flow was performed in a further eight patients, and this was found to be increased by over 100% after using the Prostaglandin.

Neither Davis not Denker reported using Prostaglandin to enhance the splenic circulation. The improved opacification of the splenic vein is important, but a striking feature was the filling of the smaller vessels of the body of pancreas. This resulted in improved opacification of the gland itself. Such detailed demonstration of normal pancreatic anatomy should exclude a disease process in the body or tail of the pancreas with good reliability.

The importance of demonstrating the patency of the superior mesenteric, splenic and portal veins in the evaluation of carcinoma of the pancreas has been emphasized by Buranasiri and Baum (1972), so that the enhancement of these structures by the use of Prostaglandin is of obvious significance (Fig. 4). Moreover, when this drug is used adequate visualization is obtained without the need to clear the spine by obliquing the patient. This is an important point, since the oblique projection results in foreshortening of the veins in the region of the head

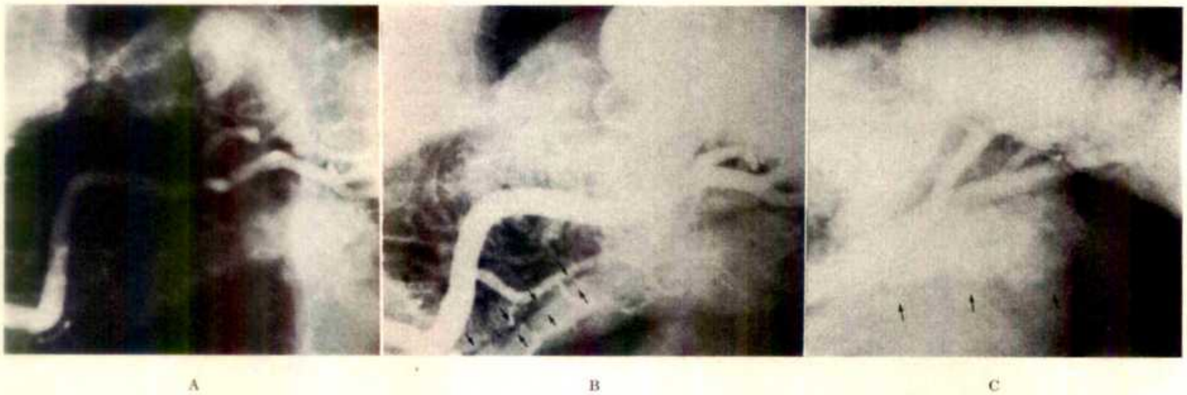

FIG. 3.

Selective splenic angiography in a 48-year-old male investigated for suspected pancreatic disease.

(A) Control study, arterial phase.

(B) After Prostaglandin injection: there is increased filling of the small vessels supplying the body of tail of the pancreas. The pancreatic duct is shown as a negative defect against the opacified gland (arrows).

(C) Venous phase, after Prostaglandin injection: the splenic vein is densely opacified, and the outline of the pancreas shown (arrows).

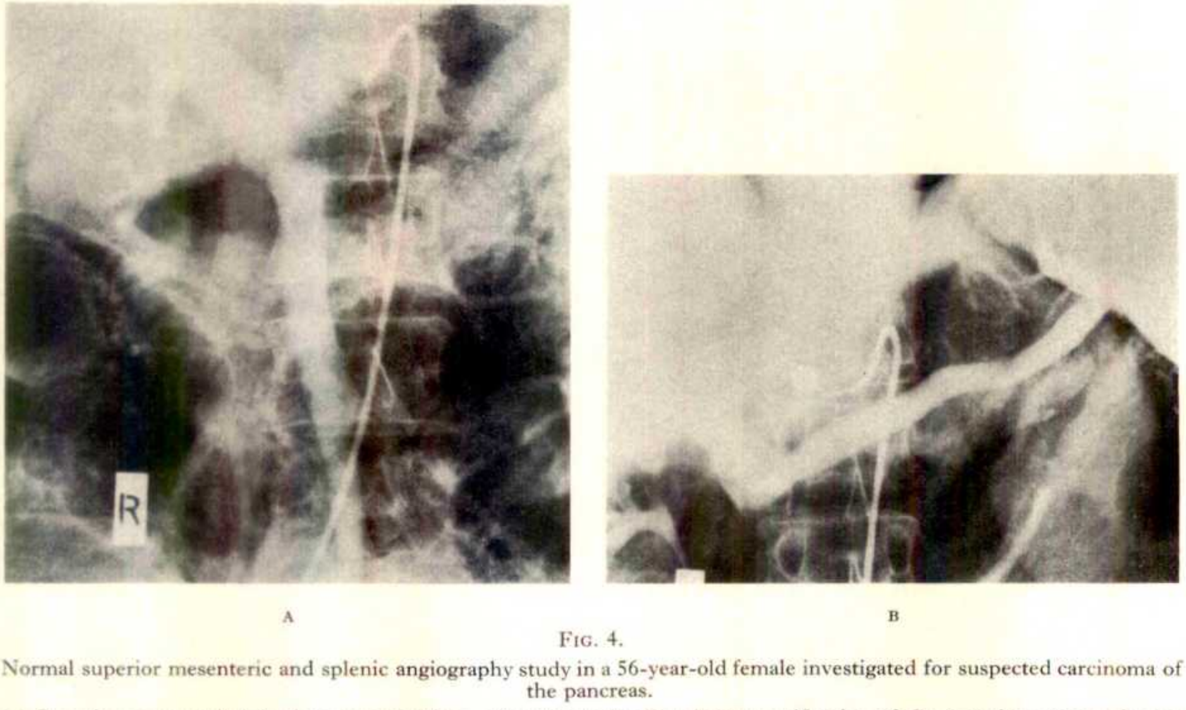

FIG. 4.

Normal superior mesenteric and splenic angiography study in a 56-year-old female investigated for suspected carcinoma of the pancreas.

(A) Superior mesenteric injection: venous phase, after Prostaglandin: dense opacification of the superior mesenteric and portal veins. No evidence of any compression.

(B) Selective splenic study, venous phase, after Prostaglandin: the splenic vein is shown in detail, and is not compressed.

of the pancreas, making evaluation of compression difficult.

Angiography is a well established technique in the investigation of portal hypertension: the demonstration of abnormal collateral veins is essential, as is the demonstration of the veins used to create a porto-systemic shunt; after surgical treatment the status of the shunt may need to be examined (Legge *et al.*, 1975). If the spleen is present, some information can be given by splenoportography, but this is less safe than arterial portography, and is associated with a high rate of false-positive findings (Bron *et al.*, 1965). However, if splenoportography is to be abandoned completely, the angiographic studies must be of consistently excellent quality, even when the patient is large, or where ascitic fluid is present within the abdomen. The use of Prostaglandin F2 Alpha should achieve such quality. Since Prostaglandin F2 Alpha is shown to improve detail of the arterial as well as the venous anatomy, while other agents reduce the quality of the arterial phase of the study, and since Prostaglandin F2 Alpha appears free of significant side effects, it seems an ideal choice as a pharmacologic aid in angiography.

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Book review

Hyperostosis Corticalis Generalisata Familiaris (*Van Buchem's Disease*). By F. S. P. Van Buchem, J. J. G. Prick and H. H. J. Jaspar, pp. ix+205, 1976. (Excerpta Medica – American Elsevier Publishing Co.)

This monograph gives an account of rare bone disease first described in 1955 by one of the authors. It is based on a clinical and pathological study of 16 cases with autopsy findings in three cases. The radiological findings are described briefly with radiographs illustrative of the salient features. The major part of the book is devoted, however, to an account of the neurological, endocrinological and psychiatric features of two cases from the series, which are dealt with in considerable detail. This section is likely to be of value to neurologists whose interest lies in the relationship of sclerosing bone dysplasias to cranial nerve function and hydrocephalus, but is of less assistance to the neuroradiologist since the application of radiological techniques to the investigation of the disease is discussed in a rather superficial manner with little emphasis on modern developments in this field.

The section dealing with the more general aspects of the condition is valuable, as must always be the case when, as in this instance, it is written by an authority with an unrivalled experience of such a rare condition. Nevertheless, the discussion is rather brief and lacking in depth and this applies particularly to the section on the differential diagnosis which is incomplete, no mention being made of such conditions as fibrous dysplasia, cranio-metaphyseal dysplasia (Pyle's disease), myelosclerosis, and sclerosteosis, all of which present a greater problem in diagnosis than does Vitamin D resistant osteomalacia which is mentioned.

It seems unlikely that many radiologists would want to possess this book though as a source of reference to a condition which they may occasionally meet, it should be available for consultation in the nearest medical library. It is also a book that should be useful in centres where there is a registry or special clinic dealing with the clinical, radiological and therapeutic aspect of skeletal dysplasias.

Ian R. S. Gordon.

1977, *British Journal of Radiology*, *50*, 256–260

Direct puncture and angiographic evaluation of axillary-to-femoral bypass grafts

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ABSTRACT

Arteriography of patients with axillary-to-femoral bypass grafts can be performed by direct puncture of the graft and passage of a catheter through the graft. This article reviews some technical considerations as well as some potential complications and how they might be minimized .Three cases are presented.

The axillary-to-femoral bypass graft is used increasingly to revascularize an extremity when the trans-abdominal approach is contraindicated. The purpose of this communication is (1) to demonstrate the radiographic appearance of the axillary-to-femoral bypass graft and (2) to describe the technique of direct puncture of the graft.

CASE HISTORIES

Case 1

In 1965 a 54-year-old female received 6000 rad externally and 100 rad internally for stage IIB adenoacanthoma of the cervix. Radiation enteritis resulted and claudication developed over five years. An aortogram showed irregularity and narrowing of the abdominal aorta and iliac arteries bilaterally. A left axillary-to-bilateral femoral Dacron bypass graft gave relief of symptoms for about five years, when right leg claudication returned.

Physical examination revealed: absent left axillary pulse; right axillary and right femoral pulse weak; left femoral pulse moderate. Clinical impression was obstruction of the femoral-to-femoral graft. Grey scale ultrasound examination demonstrated no way to discern between the area of the clotted and patent graft.

The left femoral artery was punctured below the anastomotic site. Occlusion of the left external iliac artery and patency of the axillary-to-femoral graft was demonstrated (Fig. 1). A soft "J" wire was reintroduced and passed the length of the graft. Patency of the axillary anastomosis was determined through a hand injection, and the catheter was advanced into the abdominal aorta. Using a 100 cm 6 French Teflon pigtail catheter, a midstream aortogram showed occlusion of the left external iliac artery and the right femoral-to-left femoral graft (Fig. 2). When this graft was replaced, the symptoms were alleviated.

Case 2

A 63-year-old man had had a bilateral aorta-to-femoral bypass graft placed for occlusive vascular disease. The graft was then removed because it became infected, and a right axillary-to-femoral graft was placed. Bilateral groin masses developed several years later. Occlusion of the abdominal aorta (Fig. 3A) and patency of the grafts (Fig. 3B) with aneurysmal dilations of the distal anastomoses were demonstrated. The femoral-to-femoral portion of the graft was replaced, but three months later the groin masses reappeared.

The right axillary-to-femoral knitted Dacron graft was punctured over the lateral chest wall. The femoral-to-femoral graft was occluded and the left femoral artery filled via collaterals (Figs. 4A, B). Because of the risk of false aneurysm, rupture and systemic sepsis, the grafts were removed. The perfusion of the legs was adequate after a post-operative thrombectomy of the right superficial artery. Collateral vessels had probably developed, since he could walk 200 yards without symptoms.

Case 3

A 56-year-old male with a history of bilateral carotid stenotic vascular disease was found obtunded. An arch aortogram demonstrated occlusion of the innominate, left common carotid, and left subclavian arteries, and a right femoral-to-axillary woven Dacron graft was placed. Later a right common carotid-to-left common carotid graft was inserted.

One year later the patient developed signs of cerebral ischaemia with possible graft occlusion. The axillary-to-femoral graft was directly punctured. Both grafts were patent; however, severe narrowing of both common and internal carotid arteries (Figs. 5A, B, C) was shown. Even though

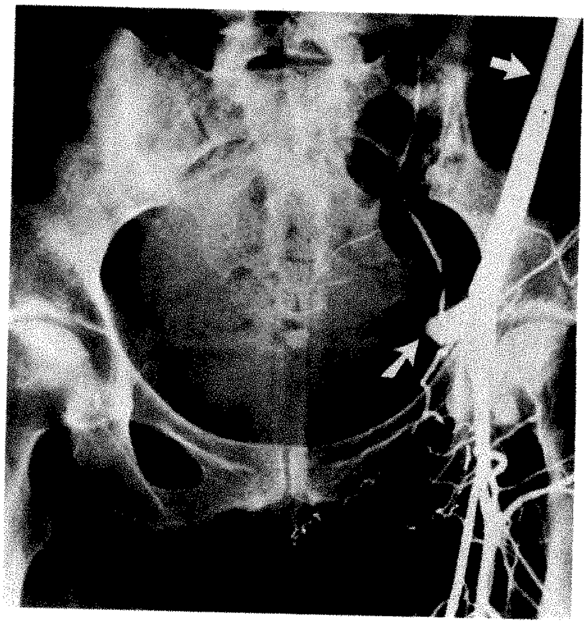

FIG. 1. *Case 1.*

Patency of the axillary-to-femoral graft (straight arrow) with occlusion of the left femoral-to-right femoral graft (slanted arrow). Occlusion of the left external iliac artery.

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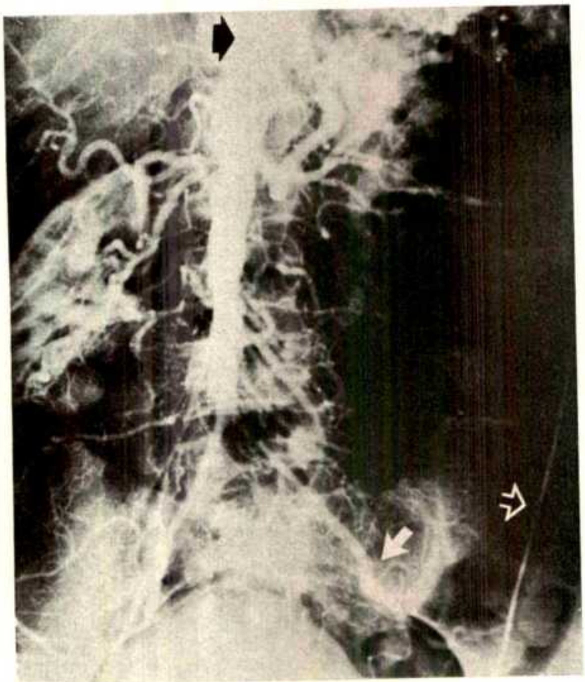


Fig. 2. *Case* 1.

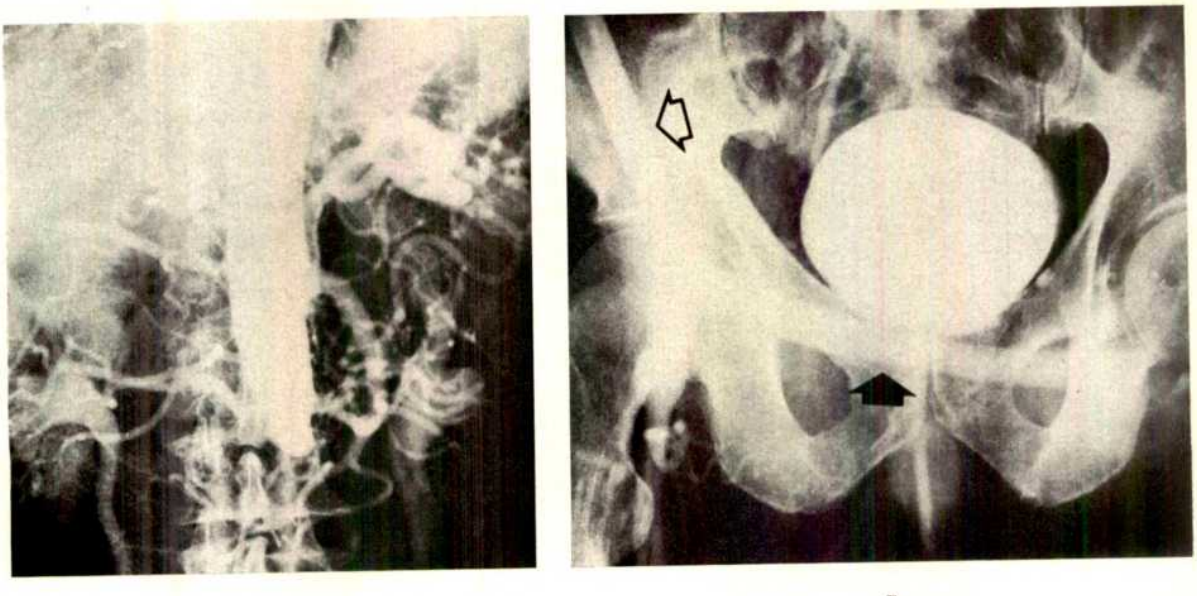
Midstream aortic injection with catheter tip near coeliac axis (black arrow). Demonstration of narrowed aorta with stenosis of both common iliac arteries and occlusion of left external iliac artery (white arrow). Catheter along left flank within the axillary-to-femoral graft (clear arrow).

further surgery was refused, the patient recovered completely.

Discussion

Axillary-to-femoral bypass grafts were described in the early sixties by Louw (1963) as well as by Blaisdell and Hall (1963). Their primary indication is the need to revascularize an extremity when the transabdominal approach is contraindicated. This includes patients with sepsis involving a previously inserted aortic graft and those who cannot withstand a major intra-abdominal vascular reconstruction because of associated illnesses (Moore *et al.*, 1971; Mannick and Nasbeth, 1968). Less frequent indications have been extra-abdominal management of abdominal aortic aneurysms in high risk patients and femoral-to-axillary grafts for arm ischaemia (Moseley and Porter, 1973).

The complications of prosthetic grafts include: anastomotic stenosis, occlusion, false aneurysm development at the anastomotic site, infection, delayed rupture, and enteric fistula. Axillary-to-femoral bypass grafts are subject to all of these complications except enteric fistulas. In addition, the axillary-to-femoral graft, because of its superficial location, may be occluded by external pressure such as a tight belt or prolonged recumbency in the lateral decubitus position (Malone, 1976).



A

B

Fig. 3.

(A) Midstream aortogram via left axillary approach which demonstrates total occlusion of the abdominal aorta.

(B) Patency of the axillary-to-femoral (clear arrow) and femoral-to-femoral grafts (black arrow).

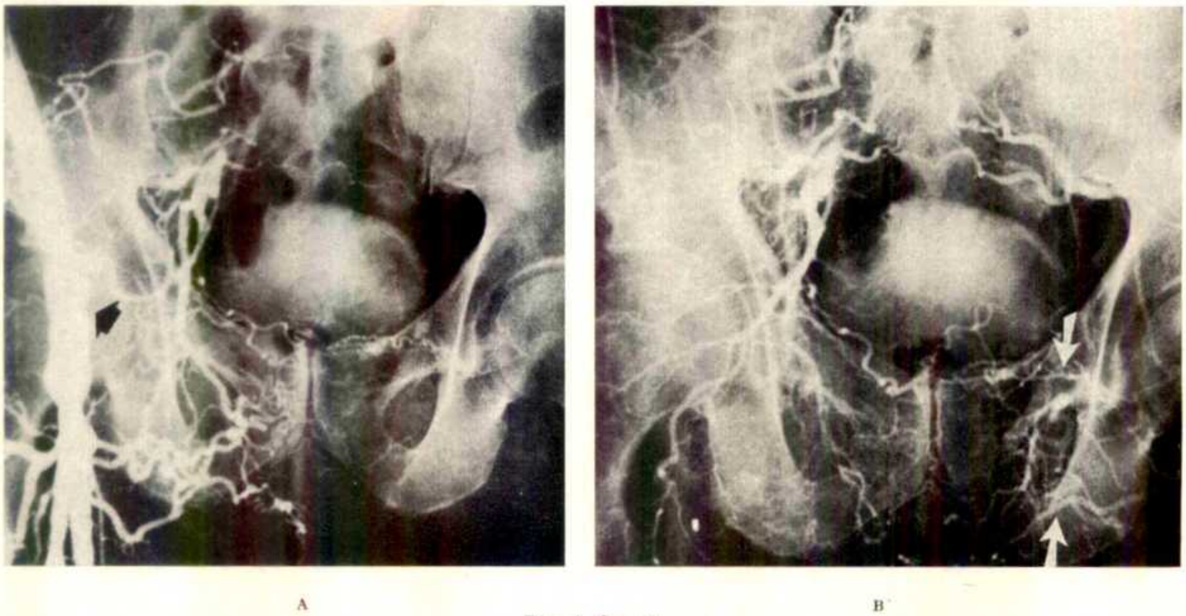


FIG. 4. *Case 2.*

Direct puncture of the axillary-to-femoral graft which demonstrated occlusion of the femoral-to-femoral graft (black arrow) with collateralization to the left side (white arrow).

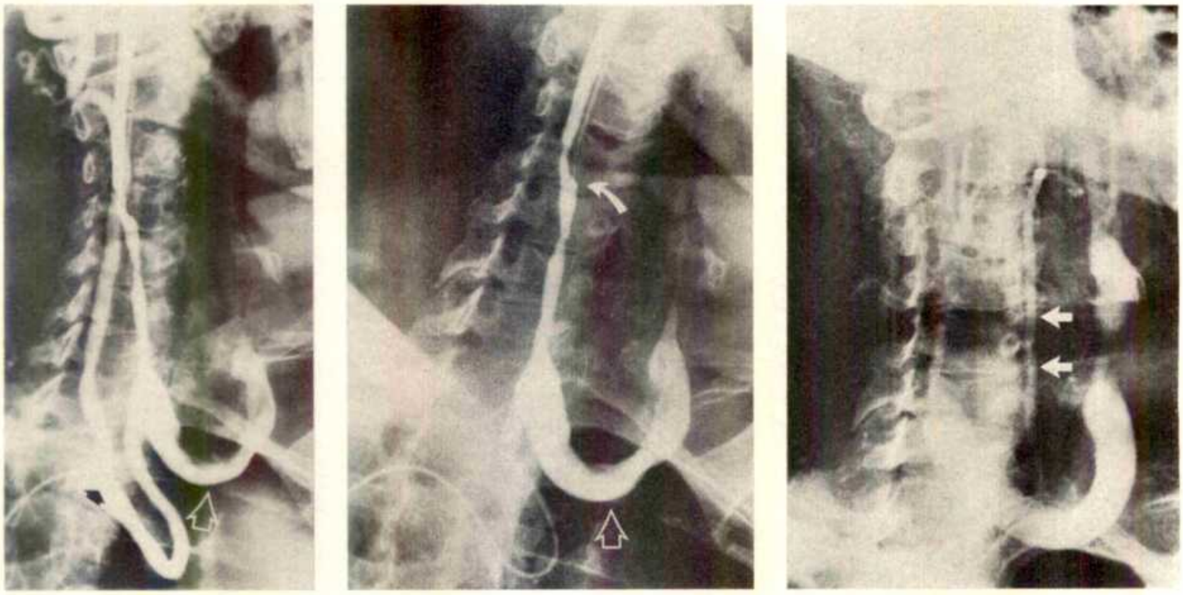


FIG. 5. *Case 3.*

Direct puncture of the axillary-to-femoral graft with catheter passed to proximal right subclavian (black arrow) artery which demonstrates patency of the axillary-to-femoral and carotid-to-carotid grafts (white clear arrow). Severe narrowing of the right common and internal carotid arteries; severe stenosis of the left carotid artery and occlusion of the right external carotid (curved white arrow) were later shown. There was no retrograde flow to the innominate artery. The left vertebral filled in a retrograde fashion (white arrows).

Although considered a dangerous procedure by many (Bron, 1971; Eisenberg *et al.* 1976), have recently reported 29 cases of direct puncture through aorta-to-femoral bypass grafts without complication. Therefore, with the concurrence of the vascular surgeons, the authors have begun, in selected circumstances, to employ direct puncture of axillary-to-femoral grafts. Any suggestion of systemic infection is an absolute contraindication to direct graft puncture. Any indication of possible local infection at the puncture site, *e.g.*, furuncles or cellulitis, is a contraindication to graft puncture in that particular extremity. Consultation with the patient's physician, vascular surgeons, and/or infectious disease specialist is recommended in any of the above circumstances where a method of approach, prophylactic antibiotics, timing of study, etc. must be evaluated. Systemic heparinization is not employed in non-cardiac catheterizations in our institution; a solution of 4000 units of lipoheparin, mixed with one litre of 5% dextrose in water, is used for flushing catheters.

Puncture

A knowledge of the altered anatomy, particularly anastomotic locations, is essential prior to puncture. Previous angiograms and operative notes should be reviewed and the patient's clotting ability should be considered with the referring physician. The proposed puncture site should be checked at fluoroscopy to be certain that a surgical clip is not in the puncture line, and visible calcific plaques should be avoided. Clips may indicate an anastomosis or former branches from the patient's own arterial system. The puncture should be into the common femoral artery below the level of the inguinal ligament.

Development of false aneurysms at the anastomosis has been linked to infection, stretching of grafts across joints, vibratory fatigue with end-to-side anastomosis, lack of supporting structures, and use of silk sutures (Moore and Hall, 1970).

If direct puncture of the graft is performed, markedly increased resistance (compared to a normal vessel wall) is encountered. This feeling has been described as "rock-like" or "going through towels". Usually only one wall is punctured. The risk of inadvertent pneumothorax or liver biopsy should be minimal, since an axillary-to-femoral graft is placed in the fascial plane between the pectoralis major and pectoralis minor muscles over the thorax and in the continuation of this fascial plane over the abdomen.

Wire and catheter advance

Post-operatively, the porous nature of Dacron permits capillary and fibroblastic ingrowth, producing a pseudo-intima composed of connective tissue, smooth muscle, elastic tissue, arterioles and capillaries. Patency and susceptibility of grafts to infection have been related to the integrity of the pseudo-intima. Experimental results suggest a minimum delay of one month and, if possible, up to four months after graft placement before a potential infectious innoculum is introdued (Moore *et al.*, 1974; Malone *et al.*, 1975).

The speed of formation of the pseudo-intima is closely related to the type of graft material. Woven Dacron grafts are tighter and therefore less porous than knitted grafts, permitting little ingrowth even after four weeks (Moore *et al.*, 1974; Malone *et al.*, 1975; Weber *et al.*, 1976). Knitted grafts may be velour or non-velour. Recent data indicate a lower infection rate for the newer types of knitted velour grafts which have a non-strippable pseudo-intima (Malone, 1976). Axillary-to-femoral grafts are usually velour knit, which is more porous and allows for faster formation of pseudo-intima. Though they are more likely to allow leaking until pseudo-intima formation is complete, pre-clotting will significantly reduce this difficulty. Non-velour knit types are usually used for aortic bifurcation grafts while woven grafts are used when excessive bleeding is evident, as in ruptured aneurysms.

To minimize the chance of disruption of the pseudo-intima, a soft, closed "J" wire always precedes the dilator and subsequent passage of the catheter tip through the graft. Before passing the catheter over the wire into the graft, the dilator is mandatory to avoid fraying of the end of the catheter. Since the passage of the dilator frequently "kinks" the wire at the graft wall, the wire is withdrawn approximately 2 cm between the exchange of the dilator and passage of the catheter into the graft. This minimizes the chance of fraying, kinking or breaking of the wire at the wall of the graft. After the catheter is introduced a short distance, a hand injection is used to rule out "subpseudo-intimal" dissection. When exchanging catheters, the use of a heparinized exchange wire (Case 1) again insures that the pseudo-intima is protected from possible disruption by a relatively stiff catheter tip.

Variations of the technique

Variations of film programming, injection speed and catheter types are often necessary in individual cases, depending on vessel calibre, location and run-off. Whenever possible, 5 French catheters are utilized to minimize possible thrombotic complications in the punctured limb (Mani, 1975). By using a 100 cm 6 French pigtail catheter in Case 1, the abdominal aortogram with runoff was obtained via the left axillary-to-femoral graft. For this approach to be feasible in taller patients, a special longer catheter may be necessary. The technique of passing catheters into the abdominal aorta from the axillary artery has been previously described (Beechley and Ranniger, 1973).

Film programming should be sufficiently prolonged to allow demonstration of late collaterals (Fig. 4B) as well as graft patency and anastomoses. As in routine lower extremity angiography, it is usually necessary to obtain the ipsilateral anterior oblique to demonstrate the femoral bifurcation (Beales *et al.*, 1971; Thomas and Andress, 1972).

Catheter removal

Because of the tendency of polyethylene catheters to stretch, they must be removed with great caution. Pulling against resistance could cause shearing of the catheter. To minimize this potential complication, a guide wire should be introduced to the end of the catheter and both catheter and wire removed together, pulling gently tangentially to the course of the punctured graft. After catheter removal, pressure should be maintained on the puncture site for 15–20 minutes. No increased incidence of bleeding at the puncture site has been reported.

Routine post-angiogram orders include:

1. minimal movement in the area of the puncture site for six hours.
2. Bed rest for eight hours.
3. Vital signs with check of puncture site and peripheral neurovascular status is evaluated and recorded every 15 min. ×4, every 30 min. ×4 and every hour ×3.
4. Maintenance of intravenous fluids until stable.

Using these procedures, we have encountered no difficulties.

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April 1977

Xeroradiography of the hand in patients with renal osteodystrophy

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ABSTRACT

The hands of 40 patients with chronic renal failure and varying degrees of renal osteodystrophy were studied. The xerograph and radiograph of each patient were compared, assessing the degree of subperiosteal erosion, and of vascular, capsular and ectopic calcification. While the changes of osteodystrophy were clearly demonstrated on the xeroradiographs, they were also seen on the radiographs, even when only minor changes were present. The authors prefer the xeroradiograph for the measurement of the metacarpal cortical thickness, because of the sharp medial border of the cortex afforded by the "edge enhancement" of this technique.

For more than a century the relationship between metabolic bone disease and renal failure has been recognized (Virchow, 1855; Lucas, 1883). The importance of this association has only recently been appreciated; advances in the treatment of renal failure have extended life expectancy, and progressive bone disease is now an important factor in limiting the full rehabilitation of many patients (Ogg, 1973).

Assessment of the efficiency of new forms of treatment and the initial diagnosis of renal osteodystrophy is often difficult since standard radiographic techniques are insufficiently sensitive until as much as 40% of skeletal calcium is lost (Simon, 1965). Because other techniques for assessing metabolic bone disease have important limitations, it was decided to compare xeroradiography with standard radiography, to assess whether or not it is a more sensitive technique.

Xeroradiography is a completely dry photographic process, producing images on plastic coated paper. These images are of low to medium contrast but because of a specific "edge enhancement" effect, resolution of fine detail is very good. The process is well described elsewhere in the literature and a full description of the technique is not included (Oliphant, 1955; Hills *et al.* 1955; Schaffert and Oughton, 1968; McMaster & Hoyt, 1971; Boag *et al.* 1971; James *et al*, 1973).

METHOD

Forty patients receiving haemodialysis for chronic renal failure were studied. Each patient had his hands both xeroradiographed and radiographed. The hand was chosen for this study because the earliest changes of renal osteodystrophy are often first observed radiologically in the fingers (Siddiqui and Kerr, 1971; Doyle *et al*, 1972); and because of the relatively high exposures required for xeroradiography it was felt that the lower exposure required for the hands was preferable to a higher one for any other region.

The xerographic image was produced on Rank Xerox selenium plates and processed in the Xerox 125 system. The best exposure required for each hand using conventional radiographic equipment was found to be 120kV and 8 or 10 mAs. The selenium plates were conditioned for contrast "B" and processed to produce a positive image mode, the density being set at "B" (Xerox, 1973).

Radiographs were produced using PE 4006 non-screen film with an exposure of 55kV and 50 mAs.

The xeroradiograph and radiograph of each patient were viewed separately looking for evidence of subperiosteal erosion, cortical striations, juxta articular rarefaction, ectopic calcification, calcification of blood vessels and sub-capsular calcification; the findings were recorded separately and compared later. The metacarpal cortical index was calculated from both images.

RESULTS

Of the 40 patients, 12 showed no signs of renal osteodystrophy by either technique. The remaining 28 patients showed varying degrees of renal osteodystrophy, with either one or more manifestations of the condition being present. It was found that the early signs of renal osteodystrophy, *i.e.* subperiosteal erosions or ectopic calcification were always more clearly demonstrated on the xeroradiograph but were invariably present on the standard radiograph. Figure 1 shows some features of renal osteodystrophy and compares the xeroradiographic and standard radiographic appearances.

The metacarpal cortical bone thickness was more easily measured from the xeroradiograph than from

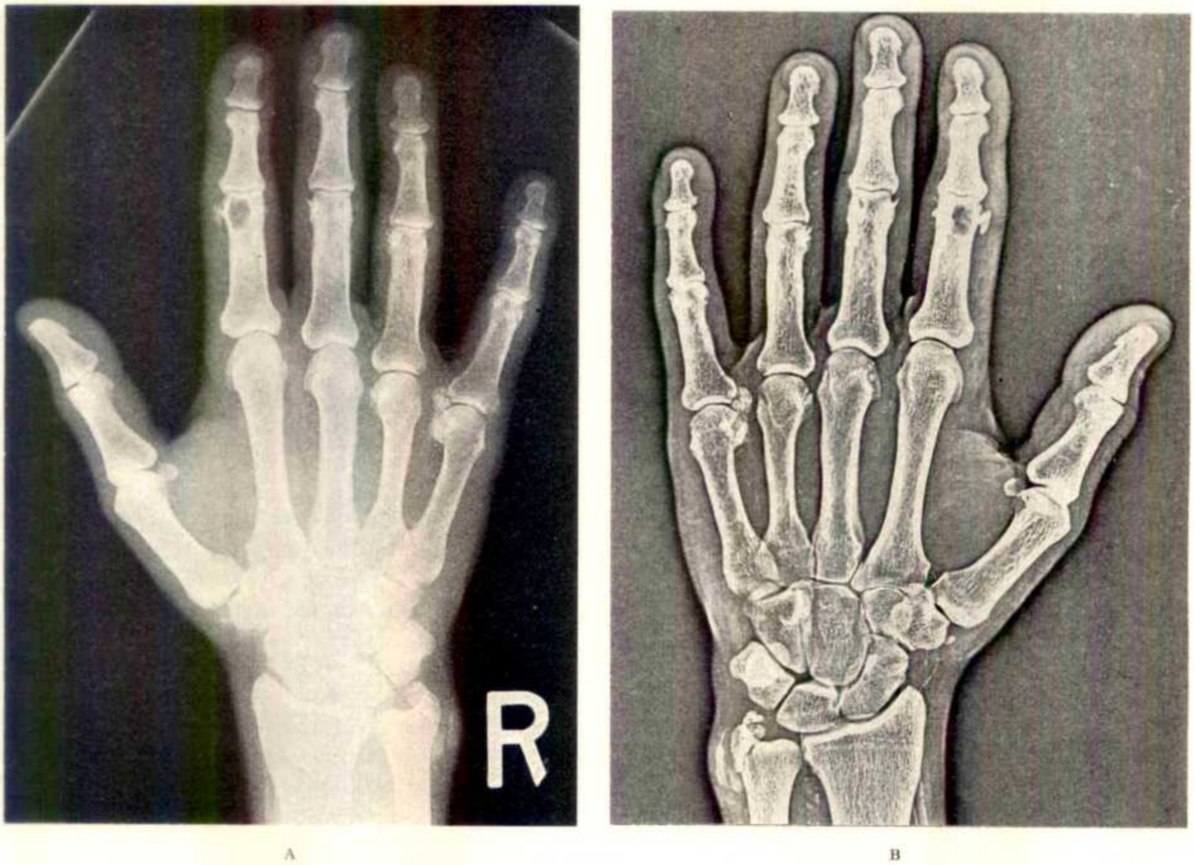

Fig. 1.

The right hand of a patient with renal osteodystrophy and secondary hyperparathyroidism (A) Radiograph, (B) Xeroradiograph (Image laterally inverted by xerographic process). Both show the vascular and ectopic calcification, but this is more clearly seen in the xeroradiograph.

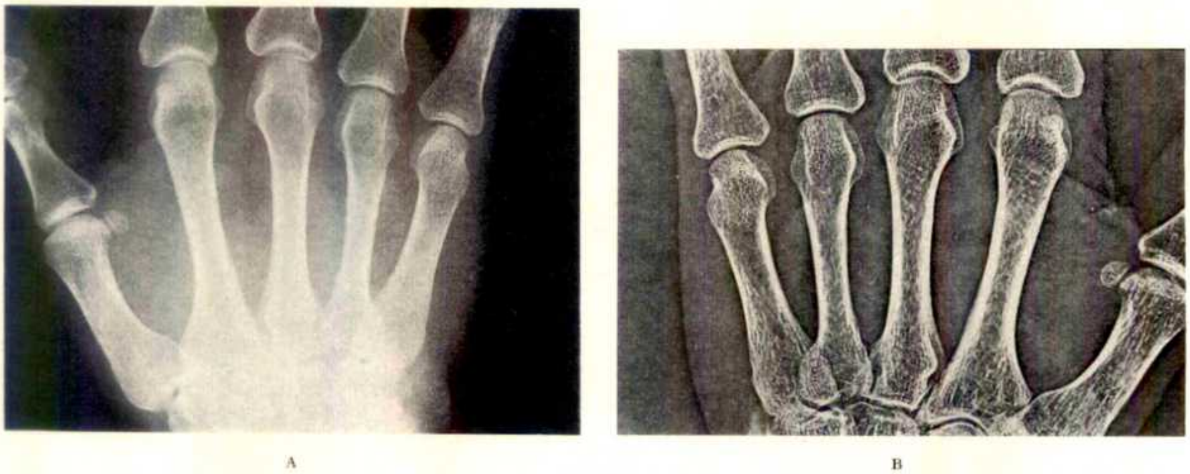

Fig. 2.

(A) Radiograph and (B) Xeroradiograph right metacarpals patient with renal osteodystrophy, showing the medial borders of the bone cortex more clearly demonstrated in the xeroradiograph.

the radiograph, as the medial border of the cortex is more clearly defined on the xeroradiograph, due to the "edge enhancement" of the technique (Fig. 2). We conclude, therefore, that measurement of the metacarpal cortical thickness is more accurate from xeroradiographs than those made from standard radiographs and hence the calculation of the metacarpal index from xeroradiographs more meaningful.

CONCLUSION

Although xerox plates are less sensitive than standard non-screen radiographic film and a higher radiation dose is required for the formation of the image, the clear image produced as a result of the "edge enhancement" effect makes xeroradiography a useful technique in the assessment of renal osteodystrophy demonstrated in the hand. Measurement of the metacarpal cortex is more easily achieved from the xeroradiograph than the radiograph. We believe that this provides a more accurate estimate of the metacarpal index.

ACKNOWLEDGMENTS

We should like to thank Dr. L. A. Gillanders for his help and advice and Dr. M. MacLeod for allowing us to study patients under his care.

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Book review

Radiology of the Small Intestine. By Richard H. Marshak and Arthur B. Linder, pp. xiv+620, Illus., 2nd edn., 1976 (W. B. Saunders Company), £28·25.

As Dr. Henry Janowitz says in his Foreword this book is a classic—the second edition is expanded and updated and contains three excellent additional chapters on metastatic cancer, angiography and the immunoglobulin deficiency syndromes. Throughout the 600 odd pages one is struck by the authors' knowledge and evident personal experience of even the rarest of pathology. The pictures are clear and demonstrate the lesions, the text is well written and lively, never boring or long winded, references are up to date and the index is easy to use. Numerous lists of differential causes of gut changes, *e.g.* malabsorption, are included which are always useful for examination purposes.

This book demonstrates how valuable the proper identification and interpretation of pathology as shown on a barium study may be and the place that a good gastrointestinal radiologist still holds in reaching a correct diagnosis.

Despite the price every department should have this book in its library, carefully guarded and protected until the next edition arrives on the market.

J. A. GLEESON.

1977, *British Journal of Radiology*, *50*, 264–265

The "negative chest radiograph" in acute pancreatitis

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ABSTRACT

Twenty-six patients with acute pancreatitis and normal chest radiographs on admission were studied. Twelve (46%) developed abnormalities in the first five days of illness. Twenty-four of the 25 patients tested developed an arterial pO_2 of less than 10.6 kPa (80 mmHg) but severe hypoxia was present in a greater percentage of patients whose chest radiology became abnormal. Blood gases and chest radiographs should be checked on a regular basis in patients with acute pancreatitis.

Respiratory complications of acute pancreatitis are increasingly recognized as direct or indirect causes of death in up to 72% of patients who die from the disease (Cameron, 1975). Pleural effusion, diaphragmatic elevation, atelectasis and pulmonary oedema have been described in the majority of patients in some reports (Kaye, 1968) while more recently, the importance of clinically occult arterial hypoxia has received considerable attention (Ranson *et al.*, 1974; Imrie *et al.*, 1977).

PATIENTS, METHODS AND RESULTS

Twenty-six patients with acute pancreatitis were selected on the basis of a normal admission chest radiograph and no history of cardio-respiratory disease. Clinical management and the routine for collection and analysis of daily aterial blood gas samples during the first week of admission have previously been described (Imrie *et al.*, 1977). Each patient had daily chest radiography performed during the initial five days of hospitalization. The series of radiographs for each patient was reported independently by one of us (J.G.D.) not involved in the clinical management of the patients.

TABLE I

Chest film changes		Follow-up
Total number of patients	26	25
No abnormality	14	22
Pleural effusion	10	0
Diaphragmatic elevation	5	1
Atelectasis	2	1
Pleural thickening	0	4
Consolidation	1	0

Changes developing radiologically during the initial five days of admission and at follow-up. More than one abnormality occurred in several patients.

The changes in chest radiology in the early phase of the illness and at follow-up three months later in 25 patients are summarized in Table I. Pleural effusions were the most frequent abnormality noted and six were confined to the left base while in four patients the effusion was bilateral. All effusions were transient and resolved spontaneously. None of the patients in this study died.

Only one patient had evidence of chest infection clinically and this was reflected in local lung consolidation and atelectasis. His sputum culture was the only positive result obtained though frequent sputum collections were made from each patient.

Another patient, who had progressively more severe arterial hypoxia, developed severe pulmonary oedema and atelectasis in the second week of illness. He was found to have pleural thickening and atelectasis at follow-up three months later, while only three other patients had minor abnormalities at this time (Table I).

Twelve (46%) of the patients developed radiological abnormalities in the first five days of illness, compared with only 14% found in a study by Fishbein *et al.* (1962), in which less frequent radiography after admission was performed.

The lowest arterial pO_2 recorded in each patient was noted and classified (Table II). It was clear that a significant number of patients who developed no radiological abnormality became hypoxaemic but severe hypoxia was present in a greater percentage of

TABLE II

pO_2 kPa	Chest film no change*	Chest film develops abnormality
> 10.6	1 (8%)	0
9.3–10.6	6 (46%)	2 (17%)
8.0– 9.3	3 (23%)	3 (25%)
6.7– 8.0	3 (23%)	4 (33%)
< 6.7	0	3 (25%)
TOTAL	13	12
Mean pO_2	9.1 kPa	7.6 kPa

Lowest arterial pO_2 recorded in first week of admission: Units kPa = mmHg × 0.133.

*One patient in this group had no arterial studies.

patients whose chest radiograph became abnormal. The mean lowest arterial pO_2 reached for the whole group was 8.4 kPa (63 mmHg) and at follow-up this had risen to 11.3 kPa (85 mmHg).

COMMENT

It is clear that a negative chest film on admission in acute pancreatitis cannot be taken to exclude subsequent chest radiograph changes and severe arterial hypoxia. This study reaffirms the importance of checking blood gases and chest radiographs on a regular basis in patients with acute pancreatitis.

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Book review

Radiologie Digestive en double Contraste. By J. Roussel, D. Regent, M. A. Bigard, pp. 286+400 figs, 1976 (Paris, Masson et Cie), 140F.

Double contrast examination of the gastrointestinal tract is not a new development in radiodiagnosis but it has gained a considerable amount of interest during the past years, especially its application to gastrointestinal segments outside the colon.

This monography reviews the results obtained by the double contrast method in the "Centre Hospitalier et Universitaire de Nancy". It is divided into three chapters which include the technical basis of double contrast examinations with specific recommendations concerning radiological equipment; the practical application and the results of this method in the oesophago-gastro-duodenal area and finally in the colon. The small intestine is not included.

This is essentially a practical book. The text is extensive and gives a detailed description of the preparation of the patient and the method of examination.

The presentation of the different pathologic lesions susceptible to demonstration by double contrast is realised mainly in the form of an atlas with numerous beautiful illustrations, accompanied by a short text including history, description of the radiological picture and results of other examinations.

One appreciates the efforts of the authors in correlating the macroscopical anatomical aspects of the lesions and their radiologic counterparts. Another aspect concerns the correlation between roentgen examinations and endoscopy which is given in most cases where this information could be relevant. This shows the close cooperation of the authors with their colleagues in the surgical and pathology departments.

The bibliography is very complete. There are no typographical errors and the quality of the illustrations is superb. They represent the most valuable aspect of this book. One may regret that the differential diagnoses of lesions of the oesophagus and the stomach are confined to the more common conditions, with a less emphasis on other conditions and also that the small intestine is not treated at all.

This book is a very good atlas and therefore highly recommended to the general radiologist who performs gastrointestinal examinations and desires to use the double contrast method routinely but also for radiology residents and gastroenterologists. Even for those already familiar with the method, this book will prove to be very useful. It should be in every radiological department.

A. BAERT.

1977, *British Journal of Radiology*, 50, 266–270

Eye dose measurements using conventional and rare-earth screens during tomography of the para-nasal sinuses

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ABSTRACT

Eye dose measurements have been performed when using medium speed conventional and rare-earth screen-film combinations during tomography of the para-nasal sinuses. The measurements show that using conventional intensifying screens with the A.P. view a total eye dose of about 20 rad may be given during an examination. This eye dose can be reduced by 98% using the P.A. position. If rare-earth screen/film combinations are employed the eye dose measured in the A.P. view was reduced by 75% of that obtained with conventional screens without detectable loss of image quality. A total eye dose reduction of about 99·5% was measured in the P.A. view with the rare-earth systems.

Increased use of tomographic techniques in studies of the para-nasal sinuses and middle ear has followed the overall increase in general radiographic procedures. Since the tomographic investigation requires repeated long exposures it can result in significant dose to patient's eyes. Although this may not be important in the context of tumour localization, there is a need to consider exposure levels to the eye during tomographic investigation of non-malignant conditions and for this reason several studies of dose distribution during tomography of the petrous bone have been presented (Dahlin *et al.*, 1973; Krohmer, 1972; Berger *et al.*, 1974; Chin *et al.*, 1970).

In this centre the Radiotherapy and Diagnostic X-ray Departments deal with roughly 40 to 50 cases involving naso-ethmoido-antral tumours every year. It is important that all areas of tumour involvement are studied radiographically with satisfactory image quality. There is also the possibility of high dose to the patient's eye during treatment. This, we felt, justified a study of eye dose during tomography of the para-nasal sinuses and investigation of ways of achieving a dose reduction for the diagnostic examination.

The purpose of this study was to measure the dose to the eye during examination under the following conditions:

(a) With linear and hypocycloidal movements and conventional film-screen combinations,

(b) With A.P. and P.A. projections, and

(c) Employing rare-earth screen-film combinations.

Whilst present methods of treatment may involve eye shielding, the delineative radiology which is an essential prerequisite of radiotherapy treatment must include the orbito-antral region. Consequently eye shielding could not be considered as a means of achieving a dose reduction.

MATERIALS AND METHOD

Linear tomograms were performed on a Philips Danatom unit and hypocycloidal tomograms on a Philips Horizontal polytome. In both units the total filtration was approximately 2 mm of aluminium, and the voltage was three-phase. The focus-film distance on the linear unit could be varied between 100 and 125 cm with an average of 110 cm and a magnification of 1.1. The focus-film distance on the hypocycloidal unit was 155 cm with an average focus to object distance of about 115 cm and magnification of 1.3. An oscillating grid of 8 to 1 ratio was used with both units.

Radiation doses to the eye were measured during examination by means of thermoluminescent dose meters. Small plastic sachets containing 30 mg of powdered lithium fluoride were placed over the patient's eye and held within a few millimetres of the cornea by means of adhesive.

The sachets of lithium fluoride were calibrated using a radium source and a pre-determined multiplicative factor applied to the results in order to correct for sensitivity of the lithium fluoride in the diagnostic energy range. The results are given in units of rads in air and have an estimated error of ±5% for measurements obtained with the A.P. examination. The results obtained with the P.A. examinations have a larger percentage error (75–90%) because these readings were of the same order of magnitude as the background readings.

During the first two parts of the study Dupont Cronex par-speed screens and Kodak RP 54 film were used. Six patients were studied on both the linear and hypocycloidal units using the A.P. projection only. Ten patients were then viewed on the

Eye dose measurements using conventional and rare-earth screens during tomography

TABLE I

Average eye dose per cut for linear and hypocycloidal movements in A.P. and P.A. examinations of the para-nasal sinuses

	Average dose per cut, mrad in air	
	A.P.	P.A.
Linear	1500	26.4
Hypocycloidal	1700	33.5

TABLE II

Average eye dose per cut for calcium tungstate and rare-earth screen-film combinations during A.P. and P.A. hypocycloidal tomography

	Average dose per cut, mrad in air	
	A.P.	P.A.
Dupont screens Kodak RP film	1700	33.5
Agfa-Gevaert MR 400 screens Kodak RP film	400	8
Trimax α8 screens XD film	550	—

linear unit in both the A.P. and P.A. projections and another ten patients were similarly viewed on the hypocycloidal unit. Typical exposures for the linear tomograms were 72 kV, 80 mA, 3 sec and 74 kV, 50 mA, 6 sec for the hypocycloidal.

In the third part of the study only hypocycloidal tomography was performed in both A.P. and P.A. projections. Medium speed rare-earth screen-film combinations were employed, namely the Agfa Gevaert MR 400 screens with Kodak RP 54 film and the Trimax α8 screens with XD film. The Agfa-Gevaert screens are an example of a blue-emitting and the Trimax of a green-emitting system. Typical exposure settings with the Gevaert screens were 75 kV, 10 mA, 6 sec and with the Trimax screen 75 kV, 15 mA, 6 sec.

Results

Average eye doses per tomographic cut during linear and hypocycloidal tomography of the para-nasal sinuses using a conventional screen film combination are given in Table I for both the A.P. and P.A. projections. For the linear movement and the A.P. view this was 1500 mrad with a range of 1000 to 3000 mrad, and for the hypocycloidal movement it was 1700 mrad with a range of 1500 to 3000 mrad. Since on average 12 cuts were taken during an examination, total eye doses of the order of 20 rad were involved with approximately 13% difference between the linear and hypocycloidal movements.

When the P.A. view was employed the eye dose was reduced to an average of 33.5 (range 20–35) mrad per cut with the hypocycloidal movement and 26 (range 12.5 to 37.5) mrad with the linear. Hence the P.A. projection produced a reduction in eye dose of about 98% compared to the A.P. projection.

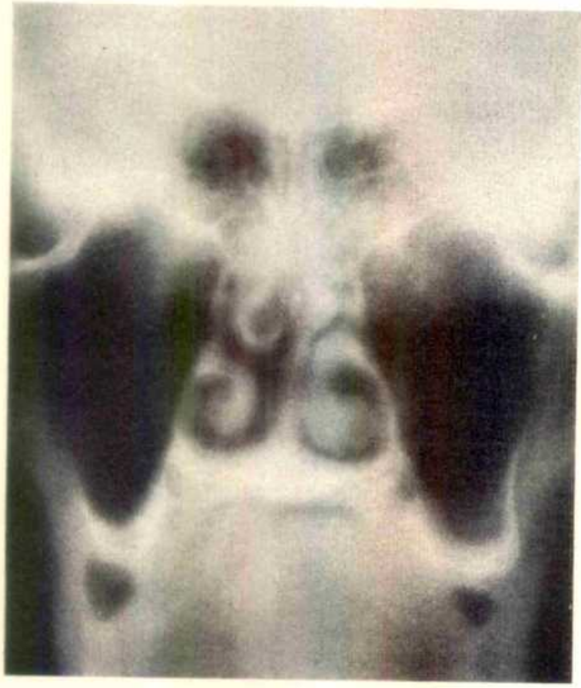
Table II gives the average dose per cut for the two rare-earth screen-film combinations using hypocycloidal movement. In the A.P. direction the Gevaert screens gave an average dose per cut of 400 (range 240 to 505) mrad and the Trimax system of 550 (range 210 to 1195) mrad per cut. These systems, therefore, produce about 70% reduction in eye dose compared with the calcium tungstate screens. When the P.A. projection was used an average dose per cut of 8 mrad was recorded with the Gevaert system (range 2.5 to 10 mrad) which corresponded to a total dose reduction of about 99.5% compared with the A.P. examination using calcium tungstate screens.

Discussion

The results presented in Table I show that similar eye doses are involved when linear or hypocycloidal movements are employed in tomography of the para-nasal sinuses. The measured values obtained in this study agree closely with those presented previously for A.P. examinations of the middle ear using hypocycloidal movement with conventional film screen combinations (Berger *et al.*, 1974; Krohmer, 1972; Chin *et al.*, 1970). Measured values shown in Table I for the P.A. projections also agree with those obtained previously for middle ear tomograms (Berger *et al.*, 1974).

In tomography of the para-nasal sinuses as well as that of the middle ear a total eye dose of 20 rad will usually be involved during an examination using the A.P. projection and calcium tungstate screens. A very large reduction in eye dose can be obtained by merely reversing the patient and using a P.A. projection. In this projection there was no detectable loss of image quality compared with that obtained in the A.P. view. This is demonstrated in Fig. 1 which shows hypocycloidal tomograms of the para-nasal sinuses at a position approximately 20 cm above table top for the A.P. projection (Fig. 1A) and 5 cm above table top for the P.A. projection (Fig. 1B).

Initially we had doubts regarding the accuracy with which centering and positioning of the cut plane could be performed in the P.A. projection.



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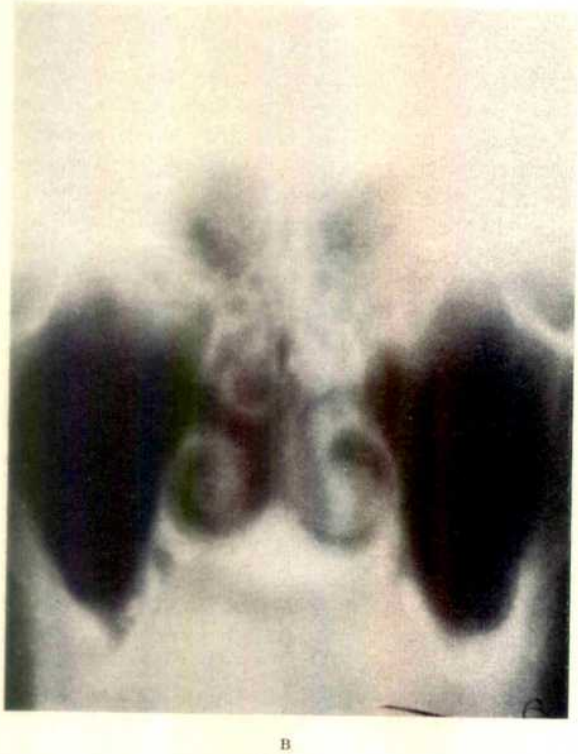


B

Fig. 1.

Tomographic images using a conventional medium speed screen film combination with (A) A.P. projection and (B) P.A. projection

However, the radiographs reproduced in Fig. 1 show practically the same tomographic image. It was possible in nearly all cases to reproduce with the P.A. examination images previously obtained in the A.P. Many of the patients examined in the P.A. position were over 60 years of age; positioning should be very much easier for children and young adults.

Large reductions in eye doses can be obtained in the A.P. projection if rare-earth screen film combinations are employed. The values measured for the green-emitting Trimax $\alpha 8$/XD screen-film combination were slightly higher than those obtained with the blue-emitting Agfa Gevaert MR 400 screens used with Kodak RP 54 film. This increase was largely dictated by the mA values obtainable on the equipment used. The same kV value was used for both systems with the 15 mA dial setting for the Trimax system and the 10 mA setting for the Gevaert system. The overall film densities were on average slightly higher for the Trimax system.

The eye dose produced with rare-earth systems during the hypocycloidal A.P. examination is approximately twice that obtained using 2 mm lead eyeshields in tomography of the middle ear (Krohmer, 1972; Chin *et al.*, 1970). Although no loss in picture quality was reported when eye shields were used in tomography of the middle ear, definite loss is observed in tomograms of the para-nasal sinuses particularly in the orbital-region where blurring residuals affect the orbito-ethmoidal imaging.

Eye doses were reduced to the limits of sensitivity of the thermoluminescent measuring technique when the P.A. projection was employed with rare-earth screen-film combinations. For this reason measurements were made only on the Agfa-Gevaert system. These measurements demonstrate that by correct choice of film-screen combination and patient positioning, eye doses can be reduced to a minimum during tomographic examinations of the para-nasal sinuses and middle ear.

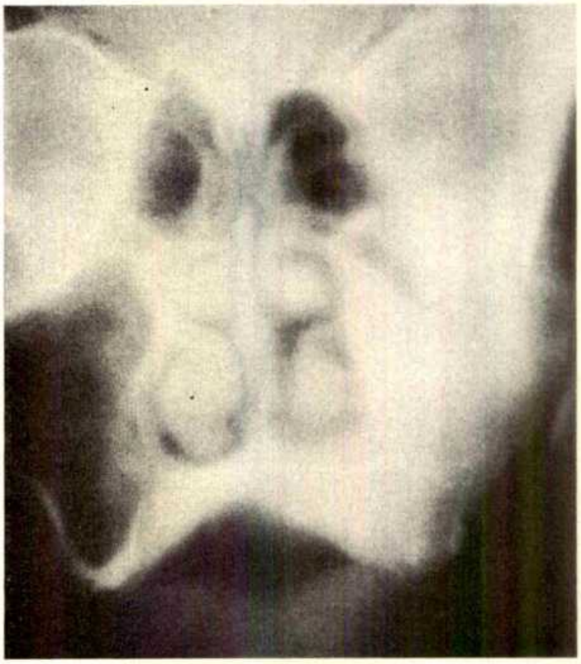
Although dose reduction through the use of faster screen-film combinations is very important, image quality must be maintained at a suitable level. Important variables in any definition of image quality are noise, contrast and sharpness. A study of the role of these factors in thin section tomography has been performed (Barnes and Witten, 1974) for conventional film-screen combinations. The conclusion drawn from this study was that more detail is visible with a combination of slow-speed film with fast screen than with a combination of faster speed film with slower speed screen. This is due to four factors: (a) a substantial reduction in quantum mottle, (b) greater blurring of mottle, (c) the greater contrast of the slower film and (d) the inherent unsharpness of the tomographic image which limits the advantage of the sharper screens. These conclusions apply when comparing the α8/XD Trimax combination of fast screen and slow film employed in the present study with the alternative α4/XM Trimax combination of slow screen and fast film of similar total speed. They need not apply, however, when comparing screens of different composition such as the conventional and rare-earth systems.

Quantum mottle is usually the main contribution to noise (Rossman, 1963) and this will be most noticeable when phosphor materials which have a high X-ray to light conversion efficiency are used with high sensitivity film. Under these circumstances the average number of X-ray photons absorbed per unit area which contribute to a given amount of film blackening is a minimum. Data presented previously (Stevels, 1975) show that most of the rare-earth phosphor materials which have been investigated have much higher luminescent efficiencies than calcium tungstate. Consequently, if used with ideal film detectors, that is films whose spectral response matched that of the screen, rare-earth systems should show a higher quantum mottle.

Because most phosphors are not used with ideal film detectors, the spectral content of the emitted light and the degree of film sensitivity plays an important part in determining the amount of quantum mottle. This type of detailed information is not available for the rare-earth systems and without it their quantum noise characteristics cannot merely be described in terms of X-ray absorption properties (Stevels, 1975).

Based purely on visual assessment the noise properties of each system were very similar in the tomograms of the para-nasal sinuses. All low contrast information which was detectable on the calcium tungstate system was also detectable on the rare-earth systems. Consequently any intrinsically different noise characteristics which may exist between the different screen-film systems have either been averaged out by the tomographic movement or they do not produce detectable changes in the structures under investigation.

The intrinsic contrast (Stevels, 1975) of film-screen combinations depends upon the variation with X-ray energy, the absorption coefficient of the screen material, the X-ray spectrum used and the contrast of the object under investigation. Recent measurements of characteristic curve (Pritchard and Hufton, 1976; Henshaw, 1975) show that the



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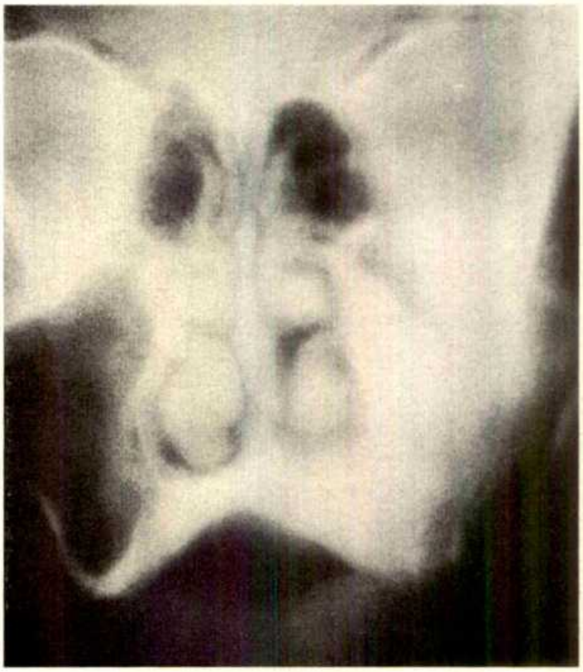

B

Fig. 2.

Tomographic images using rare-earth screen film combinations with (A) Trimax α8 screens and XD film, (B) Agfa Gevaert MR400 screens and Kodak RP 54 film.

gamma of the film-screen combinations used in this study in the range 60 kV to 110 kV were all very similar. Examples of tomograms taken with the Trimax and Agfa Gevaert medium speed rare-earth systems are shown in Figs. 2A and 2B respectively, for the same patient and approximately the same cut plane. Since it was not feasible to perform tomographic investigations on the same patient with all systems, the images reproduced in Fig. 2 were selected to represent approximately the same cut plane shown in Fig. 1 but for a different patient. Figures 1 and 2 cannot, of course, be compared directly. However, using subjective assessment of all the images produced during the investigation, the degree of contrast in the kV range employed, which affects edge definition between black, grey and white (bone), was indistinguishable between the three systems from the point of view of determining tumour spread.

Visual assessment must play an important role in any comparison of conventional with other forms of imaging systems, a fact which has been highlighted by physical measurements recently performed on some of these systems. Noise measurements in conventional and Trimax rare-earth systems (Wagner and Weaver, 1974) show that the noise power spectrum of the rare-earth system is comparable to that of the conventional system at lower spatial frequencies when measured under diffuse conditions. When measured under specular conditions, however, the rare-earth system showed more noise than the conventional system at these frequencies. Under both conditions the rare-earth system showed less noise at the higher spatial frequencies.

This raises a problem as to how the noise should be measured in a radiographic film that in practice is intended to be illuminated diffusely, but viewed specularly. It also raises questions concerning the specification of contrast, noise (a function of contrast) and signal-to-noise ratio which appear to be unresolved at the moment and may require extensive studies of observer performance.

Summary and Conclusions

Eye dose measurements were performed during tomographic examinations of the para-nasal sinuses. Using conventional calcium tungstate screens with Kodak RP 54 film, total eye doses of some 20 rad were involved in an A.P. examination. This exposure level was reduced by about 98% using the P.A. view. In most cases patient positioning and reproducibility of cut plane were straightforward with this projection.

The use of rare-earth screen-film combinations allows an eye-dose reduction of about 70% for the A.P. view. This is still roughly twice the dose level obtained using 2 mm lead eye shields in tomograms of the middle ear, but in tomography of the para-nasal sinuses eye shields are not practicable if delineation of the orbital regions is required. Based on over ten years' experience in dealing with tomograms of the para-nasal sinuses the medium speed rare-earth screen-film systems investigated were found to give adequate image quality for the range of kV normally employed. A total reduction in eye-dose of about 99.5% is possible if the medium speed rare-earth systems are used with the P.A. view.

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Tumour regression as a guide to prognosis: a study with experimental animals

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ABSTRACT

An analysis has been made of the relationship between regression during therapy and the probability of local control in a group of mice treated with single doses and fractionated doses of X rays. The tumours were first generation transplants from spontaneous mammary carcinomas in C3H mice and were irradiated with single doses, 3F/4 days, 9F/10 days, 9F/18 days or 15F/18 days. The size of the smallest radiation dose approached those encountered in clinical radiotherapy.

A significant correlation was observed between the shrinkage during the treatment period and the local control at 150 days, for three of the four fractionated schedules. A weaker correlation was observed for shrinkage within a week after single doses, and for shrinkage during treatment with nine fractions in 18 days.

It is postulated that the rate of shrinkage is an inherent characteristic of each individual tumour and does not reflect the number of cells killed. However, the shrinkage in some tumours during the course of therapy may result in more extensive reoxygenation which makes these tumours more sensitive to subsequent doses of the fractionated course.

The degree of shrinkage within the period of fractionated irradiation was found to be a useful prognostic guide to ultimate local control in individual tumours.

An evaluation of any form of experimental cancer therapy is beset by the well known problems of what can be measured and whether it is relevant. Survival of the patient is not a relevant parameter for local treatment unless the deaths are due to local recurrences and not to distant untreated metastases. Local control, for example at two or five years, is often used for comparing treatments, but patients are lost from the comparison due to early deaths not resulting from tumour in the treated area. Some information can be gained from palliative treatments of multiple nodules in the lung (Breur, 1966; van Peperzeel, 1972; Malaise *et al.*, 1972) or in subcutaneous tissue (Friedman and Pearlman, 1955; Thomlinson *et al.*, 1976), but a very limited range of doses is possible to enable measurements of regrowth to be made before the patient dies from widespread metastases. An early indicator of prognosis would obviously be very useful for comparing different forms of treatment in two groups of patients. If this observation could be made sufficiently early in an individual treatment, it might even be possible to use it for determining what further therapy was necessary for that individual. For many years the extent of tumour regression has influenced the therapist's optimism about the outcome of his treatment in that patient, but it has been difficult to prove statistically from clinical data that any correlation exists between shrinkage and prognosis.

In animal experiments a more diverse series of endpoints can be measured. Animal survival, regrowth delay, local control, or direct measurements of cell survival *in vitro* or *in vivo* after excision of the irradiated tumour are all possible. In some tumour types these different endpoints yield comparable results while in others they do not, but they are all currently in use for comparing the response to different forms of tumour therapy. In any experiment in which subcutaneous animal tumours are irradiated and left *in situ*, it has been common practise to observe the tumours at regular intervals, but for the ultimate analysis it is the time at which regrowth occurs (tumour regrowth delay), or the presence or absence of a tumour at a specified time (local control) that has been studied. Tumour regression rates have been studied by Thomlinson, who showed no difference in regression rates after large single doses in the range 3000–7000 rad (Thomlinson, 1960; Thomlinson and Craddock 1967; Thomlinson *et al.*, 1976). Suit *et al.*, (1965) also showed no correlation between regression rates and local control of spontaneous C3H mammary tumours, again after treatment with large single doses. In the same paper they presented data on patients with head and neck tumours treated with conventional fractionated radiotherapy; no significant correlation was present, but the number of patients was small.

Recently radiobiological tumour studies in mice have been extended to include multifraction treatments, with doses down to 300 rad per fraction, *i.e.* much nearer to the clinical range. In the present study the shrinkage during therapy has been analysed for comparison with the local control of the tumour at 150 days in a group of transplanted C3H mammary tumours treated with single doses or with 3, 9 or 15 fractions.

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MATERIALS AND METHODS

The regrowth data analysed were obtained incidentally in the tumour control experiments published by Fowler *et al.* (1974), which were designed to study fractionation effects on first generation transplants from spontaneous mammary tumours. Each week a group of C3H mice was implanted subcutaneously with 1–2 mm fragments of spontaneous tumour. Each mouse received one tumour on the ventral thorax. These tumours were irradiated with 240 kV X rays when they reached a mean diameter of 6±1 mm. A wide range of X-ray treatment schedules was tested, as well as treatments with neutrons or with combined X rays and the sensitizing drug Ro-07-0582. In a small proportion of these experiments the tumours were measured regularly throughout the course of therapy and at weekly intervals after the first month for at least 150 days. In most of the later experiments the tumours were observed regularly but were not measured between the day of the first irradiation and the 40th day after the middle of treatment. Because of this only a small proportion of these experiments was amenable to a retrospective study of regression rates. The details of irradiation and of the scoring procedure, together with the intercomparison of different schedules, have been published previously (Fowler *et al.* 1974, 1975). Tumours were considered as locally controlled if they were 4 mm or less at 150 days. If they were 6 mm or greater at any time before 150 days they were considered as recurrences (Fowler *et al.*, 1974).

RESULTS

The treatment using the smallest dose per fraction was, of course, that employing the largest number of fractions, *viz.* 15 fractions in 18 days. In this schedule doses of 300 to 500 rad were given daily, five times a week. Each dose group contained 10–20 animals.

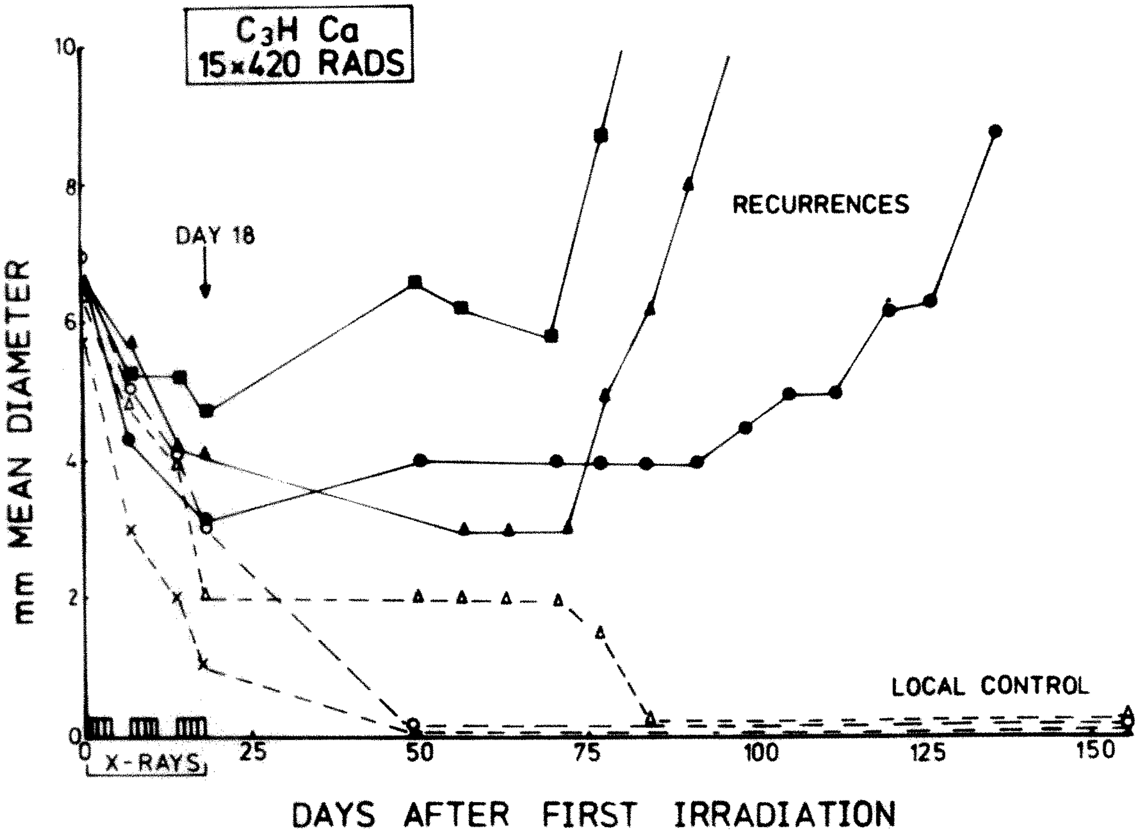

FIG. 1.

Growth curves for six C3H mammary carcinomas treated with 15 daily doses of 420 rad of X rays. These tumours were chosen as representative of the range of responses observed in this group. All six tumours shrank during the treatment period, and three were locally controlled for 150 days while three recurred between 75 and 125 days. The locally controlled tumours shrank more during the treatment period than those that subsequently recurred.

In Fig. 1, an example is shown of six of the tumours treated with 15 daily fractions of 420 rad over 18 days. The tumours were irradiated at 6±1 mm mean diameter and they shrank to varying degrees during the 18-day treatment period. No measurements were available between the last irradiation and day 49 so the minimum volume and the time at which it was reached cannot be determined for all the tumours. Three tumours recurred within 75 to 125 days, and three remained below 4 mm diameter for at least 150 days, the criterion used for local control. At the end of treatment, two tumours were less than 3 mm and did not recur later; two were greater than 3 mm and recurred; two were just 3 mm, of which one was sterilized and one recurred. This demonstrates graphically a correlation between shrinkage within the treatment period and the ultimate control probability for this selected group of tumours from the 15×420 rad group.

Figure 2 shows the results for all 69 animals which fulfilled the conditions necessary for this analysis in the 15F/18 day experiment. The mean diameter at the end of treatment is plotted against dose per fraction and the animals which were locally controlled at 150 days or which had recurrences are indicated by open or closed symbols respectively. With increasing dose the proportion of locally controlled tumours increases. The dashed lines indicate the average size at the end of treatment of the "cures" and of the "recurrences" respectively where more than two tumours are available for the average. Although at all dose levels there was a spread of sizes, the average diameter of the tumours which were ultimately controlled was smaller at the end of treatment than the average for recurrences, and this was true at all dose levels.

It is clear that for this 15 fraction schedule, tumours which regressed most during the 18 days of treatment had the highest probability of local control and tumours which regressed least were most likely to recur.

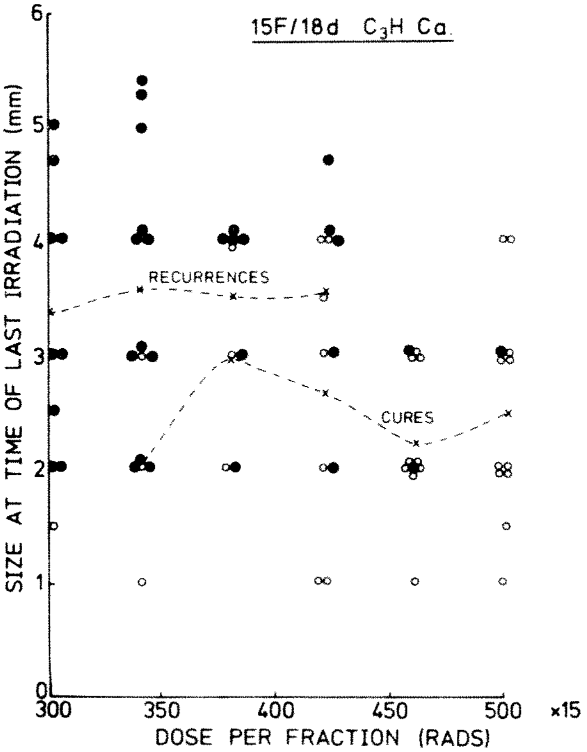

Fig. 2.

Sixty nine tumours treated with 15 daily fractions ranging from 300 rad to 500 rad. The crosses and the dashed lines represent the average sizes of the recurrences and cures. At each dose level the tumours which subsequently regrew were, on average, larger at the end of treatment than those which were subsequently cured. ○=local control. ●= recurrence.

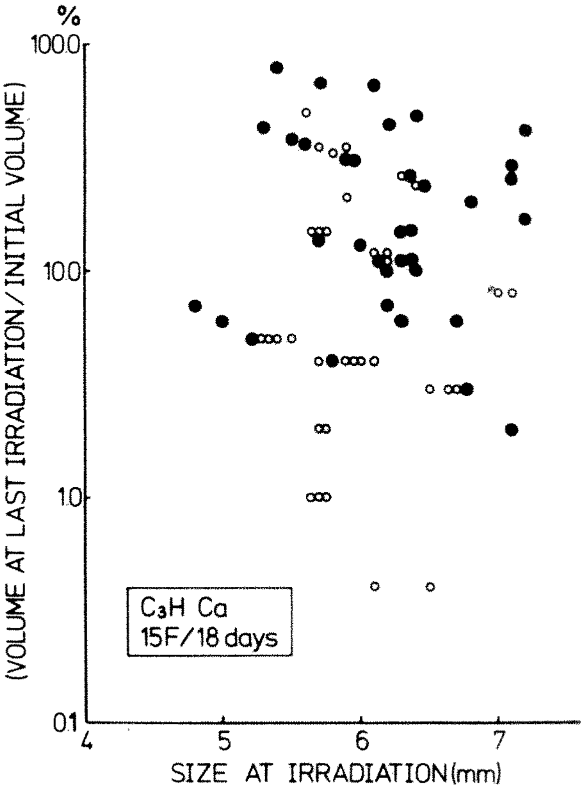

Fig. 3.

Residual volume at day 18 after 15 daily fractions, as a function of the size at irradiation. The tumours that shrank most (bottom of figure) were locally controlled, whereas those which had shown little regression subsequently recurred. There is no obvious correlation between curability and size at irradiation. ○=local control. ●=recurrence.

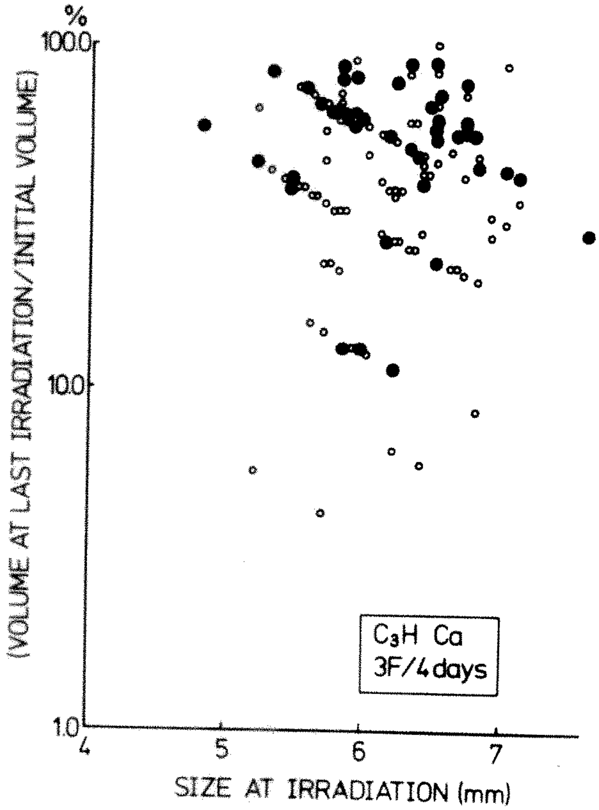

Fig. 4.

Residual volume at day four after irradiation with three large fractions of 1000–1850 rad. Again the tumours which had shrunk most were locally controlled and those which had shown little regression subsequently recurred. ○ = local control. ● = recurrence.

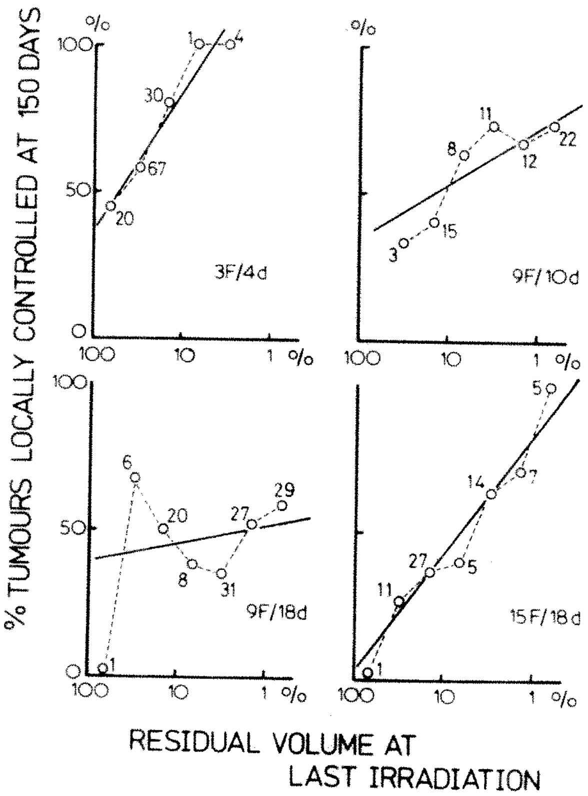

Fig. 5.

The percent of tumours locally controlled as a function of the extent of shrinkage, derived from plots like Figs. 3 and 4. The solid lines are weighted linear regression lines, allowing for the number of animals contributing to each point as indicated on each graph. A significant correlation between regression and local control is apparent for three fractions in four days, nine fractions in ten days and 15 fractions in 18 days, with a weak indication of a correlation in the same direction for nine fractions in 18 days.

The level of significance is $p < 0.001$ for three fractions in four days, nine fractions in ten days and 15 fractions in 18 days, and $p < 0.05$ for nine fractions in 18 days.

Although the tumours were selected to be within a narrow range of sizes at irradiation, the volume corresponding to 7 mm mean diameter is 2.7 times greater than that at 5 mm. This difference in volume could alter the curability of the tumour, and Fig. 2 does not allow one to distinguish between large tumours shrinking to 3 mm and smaller tumours shrinking to 2 mm. For this reason the data from the 15 fraction experiment are presented in a different form in Fig. 3. The residual volume at the end of irradiation has been calculated from the three perpendicular diameters, and this is plotted against the size at the start of irradiation. This plot again demonstrates that a higher probability of cure exists for tumours showing the greatest shrinkage during treatment, *i.e.* most of the cures are at the bottom of this figure, and most of the recurrences at the top. An inspection of the data in vertical columns shows no significant trend of more cures in tumours which were smallest at irradiation. It is the shrinkage, not the volume at irradiation, that is of major importance over the 2.7-fold volume range tested.

Similar data were available for single doses, for three fractions in four days, and for nine fractions given over ten or 18 days. All these experiments have been analysed as described above. Another example is shown in Fig. 4 for the shortest fractionated treatment régime, three fractions in four days. The degree of shrinkage was less in four days than in 15 days but the same correlation between regression and local control rate is shown by the preponderance of recurrent tumours in the upper part of Fig. 4.

In Fig. 5 the data from all the fractionated experiments are summarized by plotting the percentage of tumours which were locally controlled as a function of the residual volume at the end of treatment. For 15 fractions, all the tumours that shrank to 1% or less at the end of treatment were ultimately controlled. Conversely most of the tumours that showed little or no shrinkage *i.e.* which had a residual volume of 50% or more at the end of therapy, were local recurrences. The number of animals contributing to each point is indicated alongside the point. Increasing shrinkage correlates with increased control rates. A linear regression line has been fitted to each set of data, by weighting each point according to the number of animals contributing to it. For three fractions in four days, nine fractions in ten days and 15 fractions in 18 days there is a significant correlation between the residual volume and the probability of local control. There is a slight trend in the same direction for nine fractions in 18 days but it is hardly significant.

Figure 6 shows the data from single dose experiments. Since the volume could not alter during the short exposure to a single dose, an arbitrary time after irradiation was chosen for analysing the shrinkage. A reasonable number of animals had been measured either on day 4, 5 or 6 after irradiation and the data from these three groups are shown in Fig. 6. Again there appears to be a correlation between shrinkage and ultimate cure probability, although the number of mice at each point is rather small, and it is difficult to attach significance to the slopes. An analysis at later times, *e.g.* two or three weeks after irradiation, was not possible because the measurements were not available.

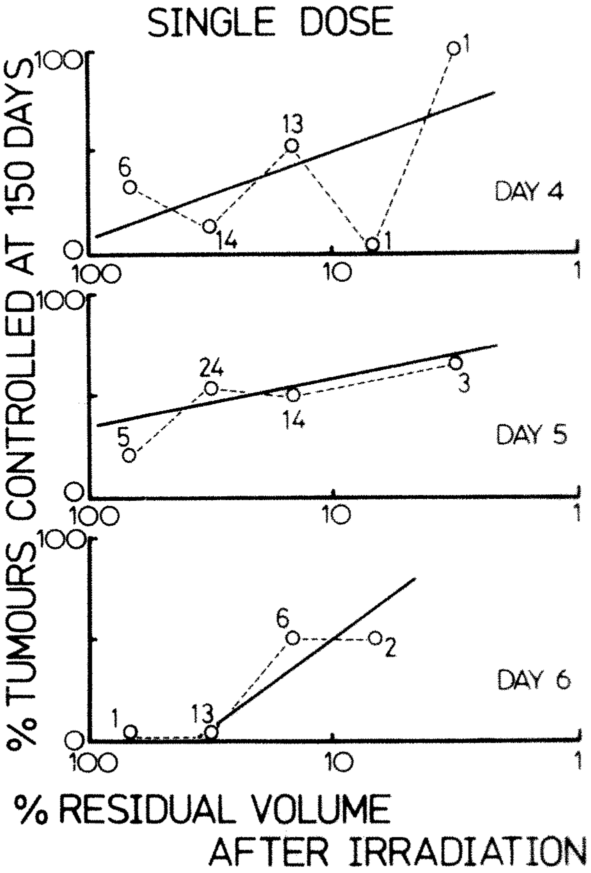

FIG. 6.

The percent of tumours locally controlled as a function of the residual volume at four, five or six days after irradiation with large single doses. The solid lines are weighted linear regression lines.

In each case there is a correlation between the local control probability and the degree of shrinkage, although most points result from very few animals. Rapidly shrinking tumours seem to have a greater probability of local control.

DISCUSSION

A correlation can be demonstrated in this group of reasonably homogeneous tumours between shrinkage during fractionated radiotherapy and the probability of local control. The tumours that shrank most before the last fraction showed the highest cure rate; the tumours that shrank least had the highest recurrence rate. As judged by the weighted regression analysis of Fig. 5 and 6, this correlation is significant for three large fractions, for nine daily fractions and for 15 daily fractions. It was less obvious for nine fractions given over 18 days. A correlation was also observed for tumours treated with single doses and examined within one week of irradiation, but because of small numbers of animals its significance is uncertain. A similar correlation between regression during therapy and local control rate can be derived from the data of Trott *et. al* (1977 and personal communication). They treated mammary adenocarcinomas with 600 rad per fraction, given at 12-, 24- or 48-hour intervals. As with the tumours analysed here the correlation was weaker for the prolonged treatment schedule ($3\frac{1}{2}$ weeks) than for the shorter schedules.

Such a correlation has been suspected by many radiotherapists but numerical data to support this suspicion have been difficult to obtain from clinical material. Suit *et al.* (1965) showed that although it was common practice at the M. D. Anderson Hospital to use residual volume at the end of therapy as the indicator for further treatment, they could not demonstrate a correlation between local control at two years and tumour mass at the end of treatment for stages T_3 and T_4 oropharyngeal carcinomas. The numbers available for analysis were small but, if anything, the trend was towards better control of the tumours that regressed slowly. Suit *et al.* (1965) also presented their data from C3H spontaneous mouse mammary carcinomas given large doses of X-rays and scored for local control at 180 days. The ratio of the volume at 14, 21, and 28 days after irradiation to initial volume was shown to have no correlation with ultimate local control. Dische (1974), however, showed a positive correlation between gross tumour shrinkage and local control at two years for his patients with carcinoma of cervix irradiated in air or with hyperbaric oxygen. A more recent evaluation of this trial confirms the correlation (Dische *et al.*, 1977). This is in agreement with the findings of Marcial and Bosch (1970) and of Grossman *et al.* (1973) for carcinoma of the cervix. Breur (personal communication) has also observed a correlation between regression and local control for cervix patients.

In other sites there has been much dispute about the prognostic significance of regression. Friedman and Rosh (1939) and Friedman *et al.* (1967) have been able to demonstrate a correlation over many years of patient study. Recently Sobel *et al.* (1976) have shown that regression within the treatment period has no prognostic significance for head and neck cancer, but absence or persistence one to three months after therapy has a strong prognostic significance.

In the clinical data there is inevitably a wide variation in histological type, grading and, to some extent, size at treatment within any group of tumours. In animal tumours which have been transplanted for many generations, the tumours are often very uniform in histology, in growth rate, and in size at irradiation. In the tumours analysed in this study, however, each experimental schedule contained tumours which had been derived from several different spontaneous mammary tumours. C3H mammary tumours are not always of the same histology, some being alveolar in form, others showing little glandular structure. The tumours had been used as first transplants from spontaneous tumours to avoid selection with repeated passage, and to stay as close as possible to the characteristics of spontaneous tumours. This degree of heterogeneity, and the small size of fractions, is generally avoided in radiobiological experiments, so that the sample studied here are more like clinical material than most experimental studies.

The factors influencing the correlation between shrinkage and control probability could be several.

1. *Intrinsic radiosensitivity*

A variation in cellular radiosensitivity could result in more cell killing in some tumours than in others, ultimately resulting in different probabilities of local control. However, as discussed by Suit *et al.* (1965) and by Thomlinson and Craddock (1967), the extent of tumour shrinkage is a very poor indicator of the number of cells killed. The doses used in the present study were all close to the level needed to sterilize the tumours and probably result in a killing of at least 99.9999% of the tumour cells. However, within the treatment period most tumours only shrank about 50%, and a very few shrank to 1%, even after 15 fractions in 18 days. The shrinkage pattern is instead a reflection of the biological characteristics of each tumour, and in particular of its host's efficiency in removing dead cells or cell debris.

The correlation between regression in the first six days after single doses suggests that there may be some relationship between radiosensitivity and the initial processes of cell removal. This deduction is at variance with that of Suit *et al.* (1965) on spontaneous mouse tumours, but they analysed shrinkage at much later times.

2. *Reoxygenation during fractionated irradiation*

It has previously been shown that the pattern of shrinkage after large single doses is different in tumours of different histology, and that this may correlate with re-oxygenation patterns and with cell loss characteristics (Denekamp, 1970, 1972). Carcinomas, which normally have very high cell loss factors, shrink rapidly after irradiation with 1–2 krad and show extensive reoxygenation of hypoxic cells within one to two days. Sarcomas, which have lower cell loss factors, do not shrink for some time after irradiation and show slower and less efficient reoxygenation (Fig. 7). Thus, although the sensitivity to single doses does not relate to initial shrinkage (Denekamp, 1972), the response to a second dose is much greater in the rapidly shrinking tumours (Howes, 1969; Suit and Maeda, 1967; Fowler *et al.*, 1975; van Putten, 1968; Kallman, 1972; Thomlinson, 1971).

This more extensive reoxygenation in rapidly shrinking carcinomas may result from the coincidence of two separate mechanisms of reoxygenation, one from reduced oxygen consumption shortly after irradiation, and the other from tumour shrinkage with concurrent reduced intercapillary distances. In a slowly shrinking rat sarcoma, RIB$_5$, Thomlinson (1971) was able to distinguish these two separate phases because of the delayed shrinkage (Fig. 7).

This apparent relationship between shrinkage and reoxygenation rate may also apply with tumours of similar histology, as studied here. The natural variability between tumours of the same type may

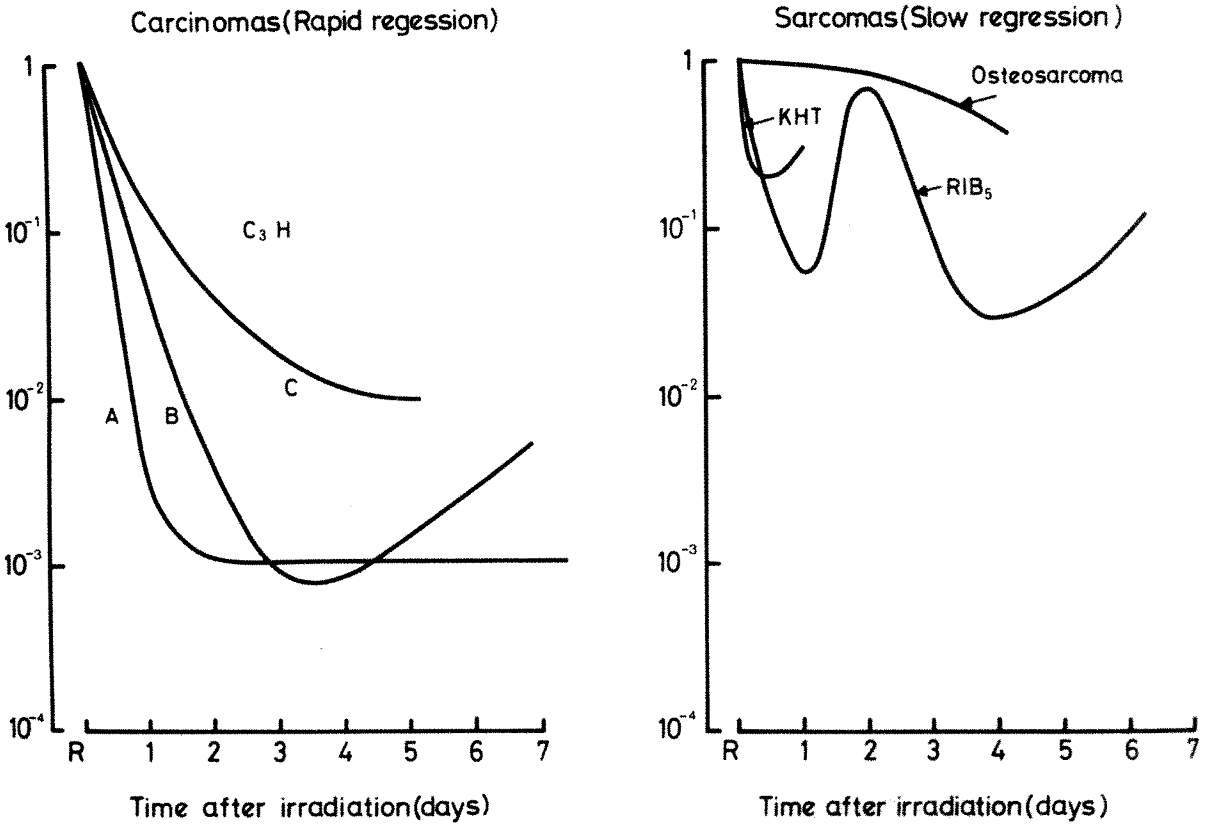

FIG. 7.

Reoxygenation patterns for six experimental tumours; the proportion of hypoxic cells as a function of time after a large priming dose of X rays. The three rapidly shrinking carcinomas show very extensive reoxygenation within one to two days, to a level well below the 5–15% characteristic of the unirradiated tumours. A, B, C are C3H mammary tumours from Fowler *et al.*, (1975); Howes, (1969) and Suit and Maeda, (1967) (re-analysed by Howes). The three sarcomas show much less extensive reoxygenation, not falling significantly below the pre-irradiation level. RIB5 sarcoma shows two distinct phases, the second of which coincides with tumour shrinkage. KHT from Kallman, (1969), RIB5 from Thomlinson, (1971) and Osteosarcoma from van Putten, (1968). Rapid shrinkage seems to correlate with extensive reoxygenation after large single priming doses.

cause the shrinkage rates, and hence the degree of reoxygenation, to vary in individual tumours. The shrinkage would then be the *cause* of a greater sensitivity to subsequent irradiation, rather than the result of greater sensitivity to earlier irradiation. This would account for correlations within fractionated schedules, but the effect would not be expected to occur with single doses.

For the longest schedule, 15 fractions in 18 days, the data were analysed to see whether the difference between shrinkers and non-shrinkers could be discerned part-way through the treatment course. No difference could be seen by the 5th fraction, but by the 10th fraction (11 days) the tumours which were ultimately controlled were smaller, on average, than those which subsequently recurred. Thus the difference in shrinkage rates needed either a lot of time, or a lot of small doses, before a separation was apparent.

3. *Differences in repair or repopulation capacities in different tumours*

Repair of sublethal or potentially lethal damage and repopulation will also influence the response of tumours to fractionated irradiation. Any increase in the extent of repair or repopulation in individual tumours would make them more difficult to eradicate. Thus repair and repopulation would have to be less efficient in the shrinking tumours than in those that shrink slowly if they are to produce the observed correlation. Repair of sublethal injury and rapid proliferation are likely to be better in cells with a good nutritional supply and oxygen status, such as tumours with an improving vasculature as they shrink during the treatment period. They are, therefore, unlikely to be contributory factors to the correlation seen here. The rather poor correlation between shrinkage and control probability after nine fractions in 18 days could conceivably be due to the counterbalancing of repopulation and reoxygenation in the two day interval between each fraction. An overall time of 18 days might allow significant repopulation in the tumours, particularly the shrinking tumours, if the longer interval between fractions was allowed.

Repair of potentially lethal damage (PLD) is by contrast less efficient in well oxygenated, well fed cells than in those that are nutritionally inadequate (Hahn and Little, 1972). Thus repair of PLD might conceivably be reduced as the tumours shrank and a more adequate vasculature was restored. If such a repair process were important it is likely to be demonstrated most readily in an experiment using a large number of fractions. Fifteen fractions in 18 days showed the best correlation between regression and control probability but three fractions in four days also showed a large effect.

All these factors depend upon the assumption of an improved vascular supply in the shrinking tumours. Since the effect of oxygen on radiosensitivity is larger than any other effect mentioned it seems likely that reoxygenation would be the dominant factor.

Fowler *et al.* (1974, 1975), showed that reoxygenation was the most critical factor in determining the response of these C3H mammary tumours to a wide variety of X-ray fractionation schedules, and that repair, reassortment and repopulation were of less importance. The present analysis suggests that even within any one schedule, the response of an individual tumour may depend on its reoxygenation status as a result of differences in shrinkage rates. The fundamental cause of these different shrinkage rates is unknown but could relate to natural cell loss processes, the efficiency of cell removal in different tumours or to the cell cycle time and hence the rate at which cell death after irradiation is expressed. The present analysis sheds no light on these basic mechanisms. It does, however, indicate that in some experimental tumours regression rates may be a useful prognostic indicator of the effects of fractionated radiotherapy. If the same were true of human tumours, slowly shrinking tumours would be the best candidates for modes of therapy designed to overcome radioresistant hypoxic cells.

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Book review

Anatomy and Physiology for Radiographers. 5th Edition. By C. K. Warrick, pp. X+294, 1976 (London, Edward Arnold), £6·75.

This is a revised edition of a book which has been available to radiography students for some time. The fifth edition is in paperback and considerably more expensive than the hardback fourth edition. It appears to be thicker but is, in fact, roughly the same number of pages. The chapter headings are larger and the type bolder and easier to read. Many more of the diagrams have been replaced by those of Mr. Hammersley, which is an improvement. But it is regrettable that mistakes have crept into this edition which were not in the previous edition.

The main changes are in the re-arrangement of the text. The advice to radiography students in the Introduction is valuable and now includes "Surface Markings" and "Functions" in the list of suggested headings. The descriptions in the text are also laid out under these headings, which is a great improvement.

The section on lymphatic drainage has been removed and is now included under each separate organ; the same applies to the chapter on "Surface Markings", which is a shame because the emphasis on topographical anatomy has been removed.

This book does not cover the subject fully enough for students to gain the complete understanding of Anatomy and Physiology which they need. But taken in conjunction with other reference books, and because it is written specifically for them, it should be a useful little book for radiography students.

Jennifer Richmond.

1977, *British Journal of Radiology*, *50*, 280–285

The reconstruction and dose-rate calculation of radium needle implants

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(*Received July, 1976 and in revised form November, 1976*)

ABSTRACT

A comprehensive computer program has been developed for carrying out the various tasks associated with radium needle implants. Data input for the program are obtained by digitizing an orthogonal pair of radiographs with an analogue tracing system. Corresponding needles in the two radiographs are automatically located, and the implant may be rotated to any desired position in three dimensional space, at the same time presenting a view of the rotation on a storage oscilloscope. Automatic determination of the mean plane of a planar implant is possible, and the dose-rate distribution may be calculated in any specified plane. A Paterson—Parker exposure rate calculation may be performed with a biological dose and treatment time correction incorporated. The program is written in Fortran and runs on a small interactive computer system.

Although the use of radium needles for the treatment of malignant disease has decreased considerably in recent years, there are still a number of sites in the body for which it is the preferred method of treatment, and the inherent difficulties of dose specification in these treatments still remain. Manual techniques for dose-rate calculation are inaccurate in situations where the distribution of the radium may be far from ideal, and the dose distribution in any plane cannot be calculated without considerable time and effort. Computer programs have been written to calculate this dose distribution (Stovall and Shalek, 1968), but data preparation has still remained a problem.

Earlier systems developed for interstitial dose calculations have used a manual method of data input. This consisted of digitizing two X-ray films by hand and relied upon the operator to locate corresponding needles on the films. Jameson (1975) has used a small interactive computer with graphical input to develop an interactive data procedure, but it is also possible to use such a system to assist in needle identification. Rapid data preparation and calculation of dose distributions can be of great assistance in the clinical situation. Dose distributions can be visualized in a variety of planes, and the effect of removing a misplaced needle from the implant can be observed immediately by the radiotherapist.

One of the main problems in dose specification with needle implants is the definition of a plane of calculation. In planar implants, this is usually at a specified distance (the treating distance) from the mean plane of the implant, and in these cases automatic determination of the mean plane should be possible. Alternatively, the problem may be solved by visualization of the implant from any direction, especially if this is done dynamically, and this would be the preferred method for non-planar implants.

SPECIFICATION OF THE IMPLANT

The conventional method employed in this department for observing the position of radium needle implants utilizes an X-ray treatment simulator, and by rotation of the X-ray head the arrangement of the needles in any direction can be viewed by means of an image intensifier coupled to a television monitor. X-ray films are then taken at the required angles. The same technique has been utilized to obtain two orthogonal X-ray films and these are used as data input for the specification of the implant. These films do not need to contain the implant in a preferred orientation, but it is better to take them in a position where no specific symmetry is seen and where all needle ends may be readily identified.

The axis of rotation of the simulator is taken to be the x axis of a cartesian co-ordinate system; thus one film will contain the x and y co-ordinates of the implant and the other the x and z. The films are digitized using an analogue tracing device connected to two analogue to digital convertors in the computer. Matching of the needles depends on the fact that the axis common to both films is the x axis, and therefore it is important that the two films are digitized in the correct orientation. The program requires that the tip and butt of each needle are digitized in that order, but the order in which the needles are digitized may be random for each film. The magnification of the films is determined from two points at a known separation (10 cm) on each film, and this is specified by the field defining wires of the simulator. As each needle is digitized its position is displayed on a storage oscilloscope, and this provides a visual check that the data input is proceeding correctly. The procedure may be repeated in the event of a mistake occurring.

After completion of the digitizing process a co-ordinate translation is applied to set the origin of the co-ordinate system to the point which is the average (x, y) co-ordinate on the first film, and the average (x, z) co-ordinate on the second film. In the ideal situation the x co-ordinates of corresponding needles in the two films would correspond exactly. Obviously this does not occur and the program continues to match needles in the two films by the following procedure.

A measure of the "goodness of matching" is obtained by adding the square of the difference in x tip co-ordinates (xt) to the square of the difference in x butt co-ordinates (xb) for any needle in film 1 and any needle in film 2. This is repeated for all possible needle combinations between the films. For example, in an implant containing N needles, N^2 matches are considered as given by

$$\text{MATCH}\,(i,j)=(xt_i-xt_j)^2+(xb_i-xb_j)^2$$
$$\text{where } i=1, 2, \ldots . N$$
$$\text{and } j=1, 2, \ldots . N$$

In this calculation both tip and butt co-ordinates are included, since it is unlikely that two needles will have the same x butt co-ordinates even if their x tip co-ordinates are very similar. A match between the two films is made on the smallest value of MATCH, this needle is then removed from each list of film co-ordinates, and the process is repeated with N-1 needles. This continues until all needles have been matched. In the reconstruction the needle with the best match is numbered 1, the worst match is numbered N.

In theory this reconstruction technique can fail and so a command is available for interchanging needle ends. If in the use of this command two different needles are specified, then the tip and butt co-ordinates of these needles on the second film are interchanged. If the same needle is specified, then the tip and butt of this needle are interchanged on whichever film the operator specifies.

The reconstruction technique uses the x co-ordinates as determined from the two X-ray films after correction for magnification. This is not the true x co-ordinate (neither are the y and z co-ordinates), due to the divergence of the X-ray beam. The true co-ordinates cannot be obtained until the match has been established as they are a function of the co-ordinates of the matching pair of needles from the two films. It is possible, in the matching process, to calculate apparent true co-ordinates for each match tested between the films. This process has not proved to be necessary as the matching process works adequately on the film co-ordinates. Inaccuracies in ignoring beam divergence are unlikely to exceed 3% as can be demonstrated by the equations reproduced in the Appendix.

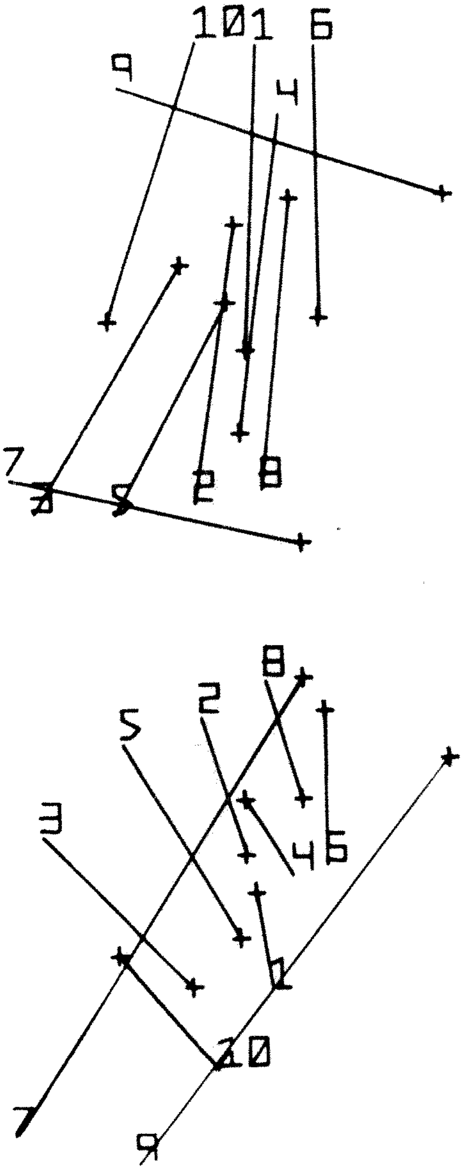


FIG. 1.

Two orthogonal views of a typical implant after reconstruction (as viewed on the storage oscilloscope).

After reconstruction the two views of the implant are displayed on the storage oscilloscope as shown in Fig. 1. The corresponding needles in each view are given the same number, and all that now remains in the specification is to input the needle types used in the implant. Currently needle types A1 to A4 and B1 to B4 are available. As the types are entered, checks are made to determine if the needle type specified by the user is sensible by comparing the length of the specified needle to that of the implanted needle. If these lengths are more than 3 mm different, the user is asked to confirm the choice before the program continues. Furthermore, if the active length of the specified needle is greater than the physical length of the implanted needle, then the selection is not allowed. All needle types may be entered automatically, or the type of any one needle may be entered by specifying the number of the needle in the implant.

SPECIFICATION OF A PLANE OF CALCULATION

The majority of radium needle implants are planar, and it is usual to calculate the dose rate for these implants on a plane parallel to (and at the treatment distance from) the mean plane of the implant. Finding this plane may be carried out by observing the rotation of the implant in any one of three dimensions on the storage oscilloscope.

Two sets of co-ordinates are held internally in the program. These are firstly the "film" co-ordinates, so that the operator may always return to the original view of the implant if desired, and secondly the "current" co-ordinates specifying the view of the implant at any time during the rotation procedure. The latter are always viewed as though the operator is looking down the z axis of three dimensional space with the x and y co-ordinates of the current view displayed. The rotation command is used to set the mean plane of the implant parallel to the x–y plane.

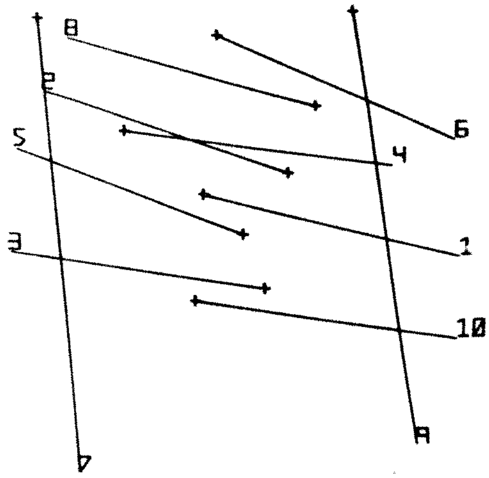
After initiating rotation the operator is presented with a view of the current needle positions (initially this is taken as the first film digitized) in "write-through" mode on the storage oscilloscope. This view is looking down the z axis and a further command allows rotation in a clockwise or anti-clockwise direction about this axis. The direction and speed of rotation are controlled by a potentiometer setting monitored by one of the analogue to digital convertors on the computer. Similar commands allow rotation in the y–z or x–z planes, with the operator viewing the implant down the x or y axis respectively. However, on stopping these rotations the view automatically reverts to the view in the x–y plane looking down the z axis. The rotation procedure is continued until the operator is satisfied that the mean plane of the implant is parallel to the x–y plane, and then he may look parallel to the implant to find a suitable distance from this plane at which to calculate the dose-rate distribution. A command is available to allow the operator to look down the x or the y axis and display the implant together with a series of lines at 0.5 cm intervals from the x–y plane. This gives some idea of the spread of the implant in addition to showing where a plane of integration could be specified. Since the development of this technique a somewhat similar procedure has been described by Jameson (1975).

Automatic calculation of the mean plane is also possible. The technique for carrying this out is similar to a technique used in crystallography for determining the mean plane of atoms in a molecular structure and this has been described by Blow (1960). Figure 2 shows the mean plane determined by this technique for the implant given in Fig. 1, together with a list of the overall needle lengths and needle types.

Although the above procedures have been described in relation to planar implants, they can also be applied to other situations where dose-rate calculations on a plane are required.

DOSE-RATE CALCULATION AND DISPLAY

The method used to calculate the dose-rate from a radium needle at any point is to segment the active part of the needle into a number of equal point sources and to use a Simpson's rule integration over all the sources. The greater the number of sources the more accurate is the calculation, and 41 sources have been used in this work. The method is



NEEDLE CONSTANTS (NO., LENGTH, TYPE)

1	35.2	A4	2	33.6	A4
3	35.0	B4	4	36.1	A4
5	33.1	A4	6	34.2	B4
7	58.6	B3	8	33.9	B4
9	57.4	B3	10	34.6	B4

FIG. 2.

The automatically calculated mean plane of the same implant.

described by Hope *et al.* (1964), but the calculation has been altered to include a tissue correction as described by Batho and Young (1967.)

A file containing the dose-rate distribution around all the available needles is created and then accessed by the integration section of the implant program. Only one quadrant of dose-rate values is generated for each needle, as the needles are assumed to be circularly symmetric about their longitudinal axis, and symmetric about a plane perpendicular to their longitudinal axis passing through the centre of the needle. The distribution around each needle is contained in a 21×21 array specifying the dose-rate up to 10 cm from the needle. The dose-rate at any point is found by linear interpolation from this array, and interpolation errors in regions of high dose-rate gradient close to the needle are avoided by storing a greater number of values in those areas.

The dose-rate distribution on the specified x–y plane can now be evaluated. At present, dose-rates are calculated for x and y values between -4 and $+4$ cm in 0.5 cm intervals, that is a 17×17 array, with a calculation time per needle of 3 sec. The dose-rate calculated at any point close to a needle may be high, and in order to improve the isodose contouring any value greater than 250 rad/hour is set equal to this value. Figure 3 shows the dose-rate distribution in a plane 5 mm from the mean plane of

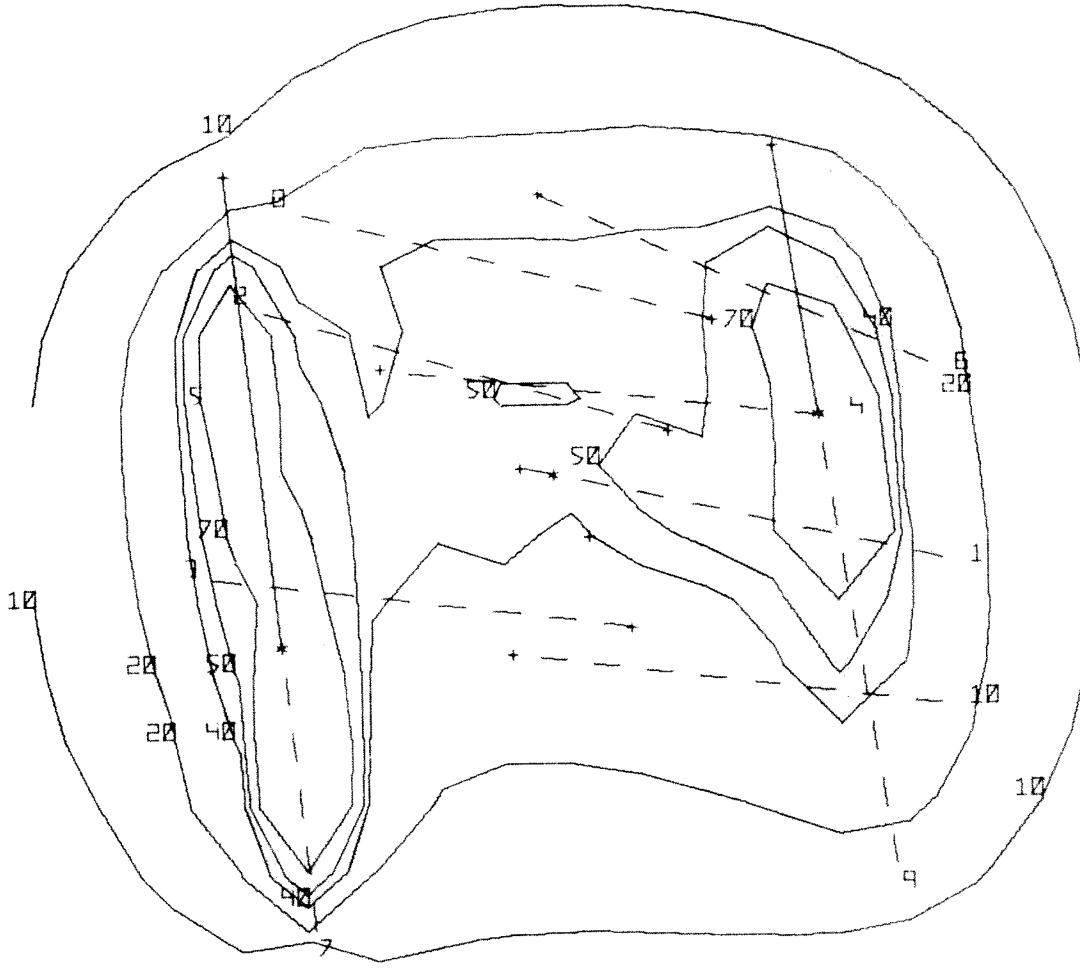


FIG. 3.

The incremental plotter output of the dose-rate distribution in a plane 5 mm from the same implant. Details of the needles are as follows.

Needle	1	2	3	4	5	6	7	8	9	10
Type	A4	A4	B4	A4	A4	B4	B3	B4	B3	B4
Length	35	34	35	36	33	34	59	34	57	35

the implant in Fig. 2, with dose-rates given in rad/hour. The needles are shown as full lines above the plane of calculation and dashed lines below the plane, with the points at which the needles cross the plane represented by *. The tips of the needles are represented by +. This dose-rate distribution has been drawn on an incremental plotter.

A command is also available to perform a Paterson–Parker dose-rate calculation. On entry to the Paterson–Parker routine the "current" positions of the needles in the x–y plane are displayed on the oscilloscope. The tip and butt of each needle are displayed with the active length represented by a vector. Four cross-wires are also displayed, two vertically and two horizontally. These may be displaced and angled under potentiometer control to define the area of the implant. The operator is asked if there are any uncrossed ends in the implant, then the area is calculated and the exposure rate on a plane 0.5 cm from the implant is given. Finally, a biological time and dose correction may be applied according to the formula given by Kirk *et al.* (1972). The prescribed dose and time are requested, and the biologically equivalent dose and time are calculated.

Summary

This program is part of a comprehensive planning system that has already been described in the literature (Redpath *et al.*, 1977). It is written in Fortran IV and runs in 14K of memory on a PDP 8 computer. The peripherals used are a Tektronix 611 storage oscilloscope, Calcomp incremental plotter, Teletype, disk and a floating point processor (for speeding up Fortran calculations). A flowchart of the program has already been given by Redpath *et al.* (1977). All the commands listed can be entered from the Teletype keyboard. The program has been in use since mid-1975 and has proved to be of considerable benefit to clinicians.

APPENDIX

The procedure used for obtaining two orthogonal views of the implant is shown in Fig. 4. The X-ray source rotates about the isocentre (0, 0, 0) at an isocentric distance of F cm. Magnifications M_1, for film 1 and M_2 for film 2 are only correct for objects lying in the plane $z=0$ for film 1 and $y=0$ for film 2.

Consider any point (x,y,z), then from film 1

$$x_{F1}=x\left(\frac{F\ M_1}{F-z}\right) \qquad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

and $$y_{F1}=y\left(\frac{F\ M_1}{F-z}\right) \qquad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

From film 2

$$x_{F2}=x\left(\frac{F\ M_2}{F-y}\right) \qquad \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

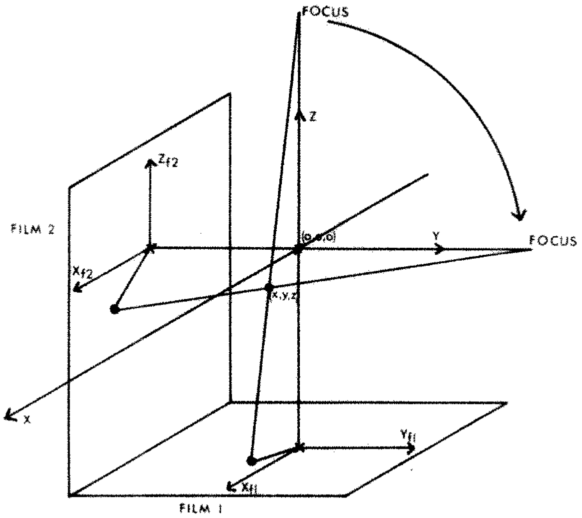


Fig. 4.

The method of producing two orthogonal X-rays of an implant.

and $$z_{F2}=z\left(\frac{F\ M_2}{F-y}\right) \qquad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

From these equations it can be easily shown that

$$x=\frac{F\ x_{F1}\ x_{F2}}{F\ M_2\ x_{F1}+y_{F1}\ x_{F2}} \text{ and } \frac{F\ x_{F1}\ x_{F2}}{F\ M_1\ x_{F2}+z_{F2}\ x_{F1}}$$

$$y=\frac{F\ x_{F2}\ y_{F1}}{F\ M_2\ x_{F1}+x_{F2}\ y_{F1}}$$

$$z=\frac{F\ z_{F2}\ x_{F1}}{F\ M_1\ x_{F2}+z_{F2}\ x_{F1}}$$

The true values for x, y and z have been approximated in the reconstruction technique by:—

$$x=\frac{x_{F1}}{M_1} \text{ and } \frac{x_{F2}}{M_2}$$

$$y=\frac{y_{F1}}{M_1}$$

and $$z=\frac{z_{F2}}{M_2}$$

The error involved in this approximation, for example in x, can be shown from equation (1), where

$$x=\frac{x_{F1}}{M_1}\left(1-\frac{z}{F}\right)$$

If reasonable care is taken to position the implant at the isocentre, then it is unlikely that z will exceed 3 cm (F = 100 cm), leading to a 3% error in the co-ordinate values used for reconstruction. After reconstruction the true co-ordinates of the implant are used (the mean value of the two x co-ordinates is taken).

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Book reviews

Radiologie de l'Appareil Digestif Opéré. By Professors H. Nahum and F. Fékété, pp. 156, Illus., 1976 (Paris, Masson), 165 F.

This book—the combined effort of a French radiologist and surgeon—is a most useful addition to the gastroenterologist's library. It is beautifully produced with exceptionally good radiographic reproductions and numerous well-labelled line drawings. The post-operative appearances found in the gut from oesophagus to rectum; in the liver, pancreas, biliary tract and portal system are described and illustrated. The text in French is sometimes a little difficult to understand for someone with a limited knowledge of the language but the quality of the X-rays and drawings and their clear demonstration of the appearances makes a text almost unnecessary. The references are up to date and include articles both from the French and Anglo-American literature. This book should prove especially useful to those commencing barium work as a ready means of checking the appearances found following surgery. It is an aesthetically beautiful book.

J. A. GLEESON.

Duodenitis. By Rodolfo Cheli and Hugo Aste, pp. 97, Illus., 1976 (Stuttgart, George Thieme Publishers), DM 34·00.

This book attempts to integrate the clinical presentation of duodenal disease with the underlying pathology both microscopic and macroscopic and the endoscopic and radiological appearances. It is an extremely difficult task for any author; unfortunately this book fails. The failure is accentuated by the laboured style of the authors and the disservice rendered to the English language by the translator. The only redeeming feature is that the text is short—a mere 97 pages.

J. A. GLEESON.

1977, *British Journal of Radiology*, *50*, 286–287

Case reports

Thymic cysts simulating loculated pneumomediastinum in the newborn

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(*Received April, 1976 and in revised form October, 1976*)

Thymic cysts are uncommon tumours of the mediastinum (Zanka *et al.*, 1965) and neck (Mikal, 1974) seen at any age. In one series (Seltzer *et al.*, 1968), a review of 200 mediastinal tumours produced only 12 cases. This is a case of apparent loculated pneumomediastinum which was found at autopsy to be due to air-filled thymic cysts.

CASE REPORT

A caucasian male infant weighing 4 240 grams was born at 41 weeks. The pregnancy and delivery were normal. At birth, however, the infant was in respiratory distress which required oxygen to prevent cyanosis. He had pelvic and bilateral flank masses. One day after birth, a contrast cystourethrogram revealed a dilated posterior urethra, a distended bladder with reflux into bilateral hydroureters and hydronephrosis. An intravenous urogram demonstrated poorly functioning kidneys. The blood urea after birth was 32 mgm-% and 55 mgm-% six days later. Chest roentgenograms taken on the first day of age demonstrated what appeared to be a loculated pneumomediastinum (Figs. 1 and 2). Follow-up examination, seven days later, showed some apparent decrease of the pneumomediastinum. At eight days of age surgery was carried out for relief of the posterior urethral obstruction and ureteral reimplantation. He died six hours post-operatively. The autopsy revealed a polyp in the posterior urethra. In the mediastinum were two prominent air-filled thymic cysts.

Pathological findings

The thymus was normal in size and position but extending from its inferior edge were two air-filled unilobular cysts measuring 0.5 cm and 2.5 cm in diameter, respectively. The larger cyst on the right was also partially attached to the pericardium and overlaid part of the right lung. Microscopically, the cysts were located between the capsule and parenchyma. There was a thin endothelial-like lining associated in parts with collagen, capillaries and small amounts of fat. There was no fluid, nor evidence of any tract leading to these cysts. The thymus was otherwise normal.

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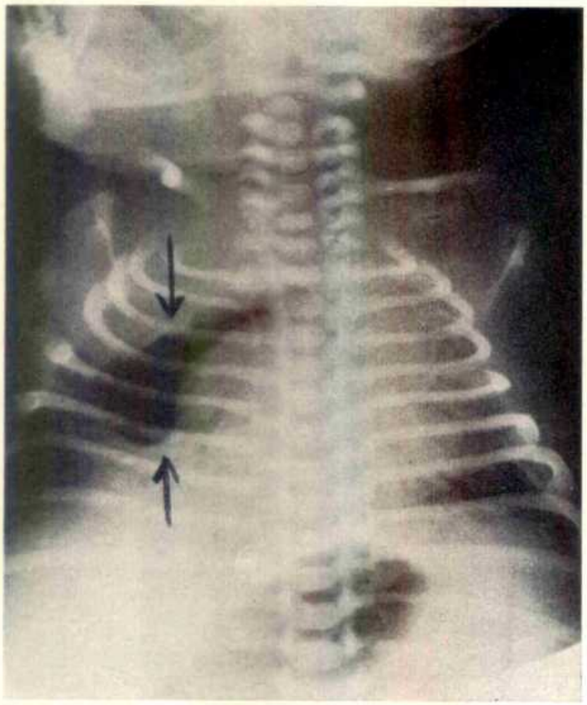

FIG. 1.

Supine frontal view. Note the appearance of loculated air, especially over the right lung.

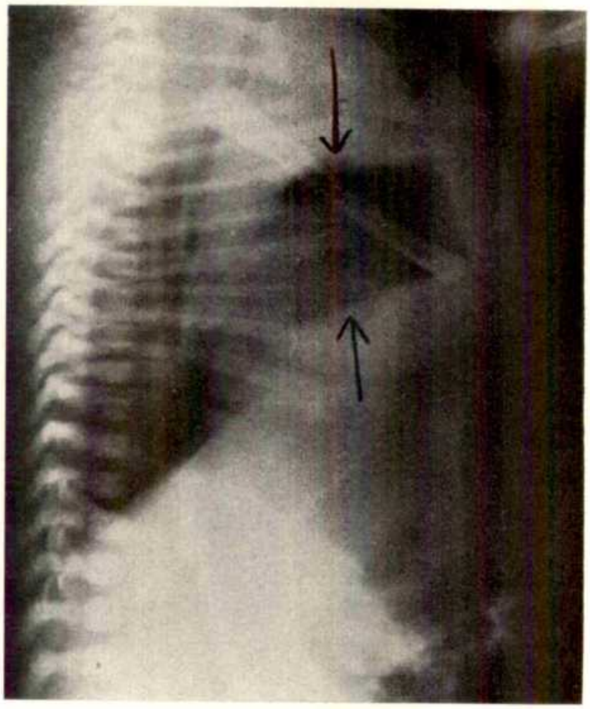

FIG. 2.

Right lateral view. The inferior border of the thymus is well outlined by restrosternal air.

DISCUSSION

The thymus begins as a sacculation from the third pharyngeal pouch during the sixth week of fetal life. Initially hollow, later solid, these buds separate and migrate caudally attached to the pericardium. The proximal portions of these stalks atrophy though remnants may persist (Arey, 1965). Cysts may occur at any site along this line of descent from the level of the mandible to the diaphragm. These cysts are usually filled with yellow fluid or blood. A true thymic cyst is lined with primitive respiratory epithelial cells of entoderm origin.

Air-filled mediastinal thymic cysts have not been previously reported. No positive pressure apparatus was used to assist resuscitation in this case. One possible explanation for the presence of air is the initial vigorous respiratory movements which may have forced air through tracts leading to these cysts and displaced their fluid. No tracts were discovered in this case.

Sometimes loculated pneumomediastinum cannot be differentiated from pneumopericardium (Caffey, 1963.). To this differential may be added the rare air-filled thymic cysts.

ACKNOWLEDGMENTS

We wish to acknowledge with gratitude the assistance of Dr. Graham Mortimer, Dr. Karl Bullivant and Mr. Des Rillstone.

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Comparison of liver scans using ^{113}In^{m}-colloid and ^{99}Tc^{m}-phytate in a patient with hepatic metastases and enlarged spleen

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Technetium 99m-phytate has been reported as a suitable agent for liver scanning (Subramanian *et al.*, 1973; Sewatkar *et al.*, 1975). It has the advantage over ^{113}In^{m}-colloid kits and commercial ^{99}Tc^{m}-sulphur colloid kits of only requiring single stage preparation. From dosimetry data (MIRD Dose Estimate Report No. 3, 1975; Sewatkar *et al.*, 1975) it is clear that uptake in the spleen is greater for the colloid preparations than for ^{99}Tc^{m}-phytate. We feel that the following case provides an informative comparison.

CASE HISTORY

The patient, a 67-year-old woman, was admitted with a two month history of loss of appetite and weight and pain in the right upper quadrant of the abdomen. An epigastric mass was present with clinical enlargement of the liver. This was tender and felt irregular.

A scan using ^{113}In^{m}-colloid (Radiochemical Centre, Amersham) showed massive uptake in the spleen and no activity over the liver (Fig. 1). A second scan, a week later, using ^{99}Tc^{m}-phytate (Internuclear Ltd.) although still showing uptake in the spleen gives a useful hepatic scan (Fig. 2).

FIG. 1.
A.P. liver scan using ^{113}In^{m}-colloid (3.3.76).

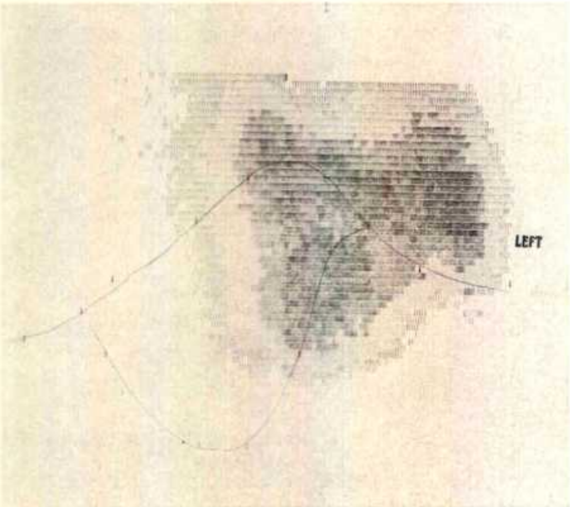

FIG. 2.

A.P. liver scan using ^{99}Tc^{m}-phytate (11.3.76). Each scan is a black and white reproduction of a colour print-out and the pencilled lines represent the costal margin and palpable liver edge.

Following the patient's death post-mortem examination showed that liver was extensively infiltrated by metastases, particularly the right lobe. The deposits were confluent at the porta hepatis. The spleen weighed 205 g but was otherwise normal.

DISCUSSION

Where diffuse liver disease with splenic enlargement is present a large proportion of the scanning agent is likely to be concentrated in the spleen. We feel that this case demonstrates a distinct improvement in hepatic uptake of ^{99}Tc^{m}-phytate over ^{113}In^{m}-colloid. If comparative trials substantiate this impression we believe that ^{99}Tc^{m}-phytate, bearing simplicity of preparation in mind, may be the agent of choice in liver scanning.

ACKNOWLEDGMENTS

We are indebted to Dr. J. Taaffe for permission to publish this case, and to Mr. Dun and the Department of Medical Illustration, Northampton General Hospital, for preparing the figures, and to Internuclear Ltd. for supplying the phytate kit.

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SUBRAMANIAN, G., MCAFEE, J. G., MEHTER, A., BLAIR, R. J., and THOMAS, F. D., 1973. ^{99m}Tc-stannous-phytate —a new *in vivo* colloid for imaging the reticulo-endothelial system (Abstract). *Journal of Nuclear Medicine, 14,* 459.

Book review

The effects of the skull upon the spatial and temporal distribution of a generated and reflected ultrasonic beam. By D. N. White, J. M. Clark, G. R. Curry and R. J. Stevenson, pp. 81, 1976 (Kingston, Ontario, Ultramedison), $10.00.

The absence, until recently, of satisfactory imaging techniques for the brain was doubly unfortunate in the sense that it channelled much of the early effort on ultrasonic techniques into largely abortive work on that organ. The present book, which really consists of a series of six related papers reporting the findings of an extensive set of experimental investigations carried out by Prof. White and his colleagues, provides a graphic account of the reasons for this disappointment. The physics of ultrasonic propagation through the irregular and multilayered structure of the skull is such that considerable distortion of spatial information is liable to be produced in any imaging process. For anyone, however, who is brave enough to accept the challenge that this situation presents in the accomplishment of a viable diagnostic technique, this slim volume will be an invaluable source of data and ideas.

C. R. HILL.

1977, *British Journal of Radiology*, *50*, 289–290

Short communications

The possibility of monitoring patient position during treatment using the transmitted X-ray beam

By D. H. Fredrickson, Ph.D., J. B. Whitton, B.S., and C. J. Karzmark, Ph.D.

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(Received September, 1976 and in revised form December, 1976)

It is generally recognized that a major problem in the radiation therapy of cancer is failure to control the local tumour (Suit, 1969). This failure is principally due to the inability to deliver a lethal dose to the tumour while sparing the surrounding normal tissue (Paterson, 1948). Future progress in solving this problem will come from improvements in tumour localization and dose distribution over the target volume. The dose distribution is influenced by immobilization error and patient movement. It is with this that we are concerned in this note.

During the past few years we have witnessed a rapid increase in new uses of the information in transmitted radiation beams. The recently available computerized tomograph systems which reconstruct density distributions of transverse sections of the human body are based on the information content of transmitted photon beams. We have been studying the feasibility of using the information in a transmitted megavoltage X-ray therapy beam to monitor patient position dynamically during therapy. At this time we are assessing whether this information pattern can be used during the treatment session to ensure that the tumour is correctly positioned with respect to the radiation beam. This would be done by a closed digital servo loop under computer control. The film study we are reporting was made to determine which tumours would yield the most information in the transmitted beam.

TECHNIQUE

Kodak Type RP/V film, which has acceptable linearity and sensitivity (Haus and Marks, 1973), was exposed during normal treatments of 17 patients in both 4 and 6 MV transmitted X-ray beams. There was no significant difference in the response of the film for these two energies. A steel screen 1·6 mm thick was placed in front of the film to reduce the scattered X rays and therefore produce a sharper image. The screen-film package was located 20–30 cm from the patient on the exit side of the beam at target-film distances of 100 to 150 cm. The exposed films were scanned on an automatic film densitometer (Artronix model 1705) and isodensity plots were made. Of 17 port films obtained, 13 were for lesions in the larynx, pharynx and oral cavity. The remaining exposures were for whole brain, chest, pelvis and cervical spine treatments. The scanned films were analysed by first eliminating the penumbral region and then identifying optical density maxima and minima and measuring the density gradients associated with these. After eliminating the penumbral region, which is not itself useful, from the analysis, we found that over the optical density range encountered, dose was a linear function of optical density to within an error of less than 10%. Consequently, we describe our results in terms of optical density.

DISCUSSION AND CONCLUSIONS

The largest density variation found was 35% in the neck region. In general, as the patient dimension along the beam central axis increases, the density variation in the transmitted beam pattern decreases. At megavoltage energies, air cavities show up more clearly than bone. An additional feature which can produce a large density variation across the film is "spill", *i.e.* that portion of the incident beam which passes outside the patient's body contour. For these reasons the largest density variations were seen in the head and neck region and, to a lesser extent, in the chest. It is a happy coincidence that the region showing the greatest density variation and therefore having the most potential for automatic positioning control is also the site of tumours having steep dose-response gradients. Hence, it is in this region that immobilization is most critical (Goitein and Busse, 1975).

Density gradients were measured and averaged over 1 cm intervals. Typically, in the chest and head and neck regions, they are of the order of 10–15% per cm. Figure 1A shows the densitometer scan for an irradiation of Waldeyer's Ring. The air

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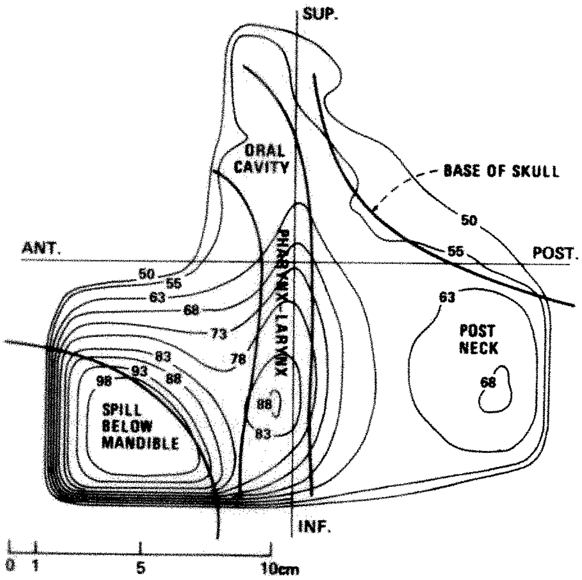
This work has been supported by Research Grant CA 05838 and one of us (D.H.F.) by a Fellowship from The National Cancer Institute, N.I.H.

1977, *British Journal of Radiology*, *50*, 290–293

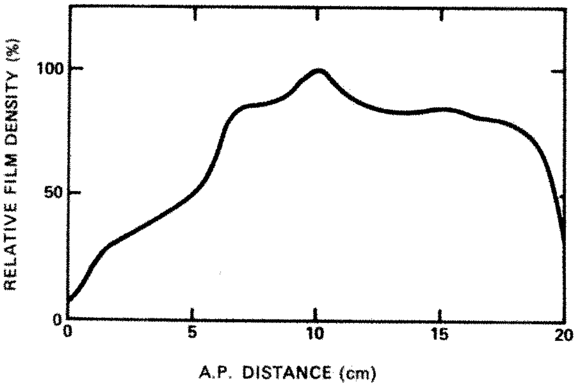


A

Fig. 1.

(A) Isodensity scan of 6 MV port film for Waldeyer's Ring treatment. The film density gradients in the region of the larynx and below the mandible are 13% per cm maximum. The posterior neck region with gradients less than 3% per cm are of little or no value for our purposes. Smooth curves have been added to identify important anatomical regions. The numerical density values identified have been normalized to 100% just below the mandible. The scale incorporates a magnification factor of about 1·2 for films of the head.

passages of the pharynx and larynx are readily apparent, as is the region of "spill" below the mandible. Figure 1B is the optical density profile on the film obtained from a scan along the A.P. line of Fig. 1A.



B

Fig. 1.

(B) Film optical density profile from a scan along A.P. line of Fig. 1A. (Normalized at 100% at point of maximum density along scan.)

In conclusion, lesions in the neck region appear to offer the greatest potential for patient positioning and monitoring schemes based on the information in the transmitted therapy beam. The transmitted beam is also being examined with a 4×4 matrix of ionization chambers.

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Enhancement of X-ray induced potentially lethal damage by low temperature storage of mammalian cells

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Since most chemical and biochemical reactions are temperature dependent, one might expect temperature to influence the proper control of metabolic processes affecting survival. For example, temperatures both above and below 37°C reduce the plating efficiency of mammalian cells (Love *et al.*, 1970; Nelson *et al.*, 1971). Incubation of mammalian cells above 37°C, both before and after X irradiation, increases their radiosensitivity (Ben-Hur *et al.*, 1972). Non-optimal temperatures have also been shown to decrease the capacity of cells to repair both sub-lethal and potentially lethal damage (Ben-Hur *et al.*, 1974; Li *et al.*, 1976; Winans *et al.*,

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1972). In contrast to these increased killing effects, post-irradiation survival of cells was shown to be enhanced if the cells were subsequently stored at low temperature (Whitmore and Gulyas, 1967). This result is analogous to liquid holding recovery seen in micro-organisms.

In the course of studying the survival response of mammalian cells as a function of intra-DNA radioisotope decays at 4°C (Burki, 1976; Koch and Burki, 1975), where the cells had to be stored to accumulate isotopic damage, we needed to quantify the modification of X-ray induced damage by prolonged cold storage. Although we expected that the damage would be decreased because of the repair of potentially lethal damage (Whitmore and Gulyas, 1967; Hahn and Little, 1972; Little, 1973), we found a consistent enhancement of X-ray induced damage when cells were stored after irradiation at 4°C. This enhancement is apparently not caused by experimental differences between the above cited work and this paper.

Materials and Methods

V79–S171–W3 Chinese hamster fibroblasts were maintained in exponential growth phase by twice weekly transfers using Eagle's basal medium (Hank's salts) with 15% fetal calf serum (medium and trypsin supplied by GIBCO). For most experiments, cells were detached by 0.05% trypsin, plated onto 60 mm glass dishes containing 5 ml of medium and incubated for 1.5 hours at 37°C for attachment. The cell density was chosen to give approximately 100 survivors after the radiation dose. The dishes were then sealed in air-tight aluminium chambers and the atmosphere inside replaced by a mixture of 95% air and 5% CO_2 (Koch and Painter, 1975). The aluminium chambers were then cooled to 0°C (time for temperature equilibrium of the medium in the dishes was 15 min) and irradiated (at 0°C) using a GE Maxitron (300 kV, 20 mA, h.v.l. 1.62 mm Cu) at a dose rate of 170 rad/min. After irradiation the chambers were stored for varying lengths of time at between 0°C and 4°C, and the dishes were then removed from the chambers and incubated at 37°C for one week. The chambers could also be irradiated at room temperature and then stored at room temperature (20–23°C) or 42°C after which the dishes were incubated at 37°C for colony growth. In some experiments the cells were spun out of the trypsin and resuspended in Ca^{++} and glucose-free phosphate buffered saline (PBS) at a density of about 10^5 cells/ml. They were then cooled to 0°C and irradiated and stored for varying lengths of time in suspension before being plated into fresh medium for colony growth (Harris *et al.*, 1975). Colonies were stained and counted with the survival criterion being a colony containing at least 50 cells.

Results and Discussion

Cold storage after irradiation caused a continuous decrease in survival with time, the effect increasing with initial dose (Fig. 1). There seemed to be a biphasic nature to the cold response with a rapid decrease in survival followed by a slower decrease after two to six hours. The survival of unirradiated control cells stored at 4°C was unchanged over the 30 hour period of the experiments. Similar decreases in survival were found if the cells were

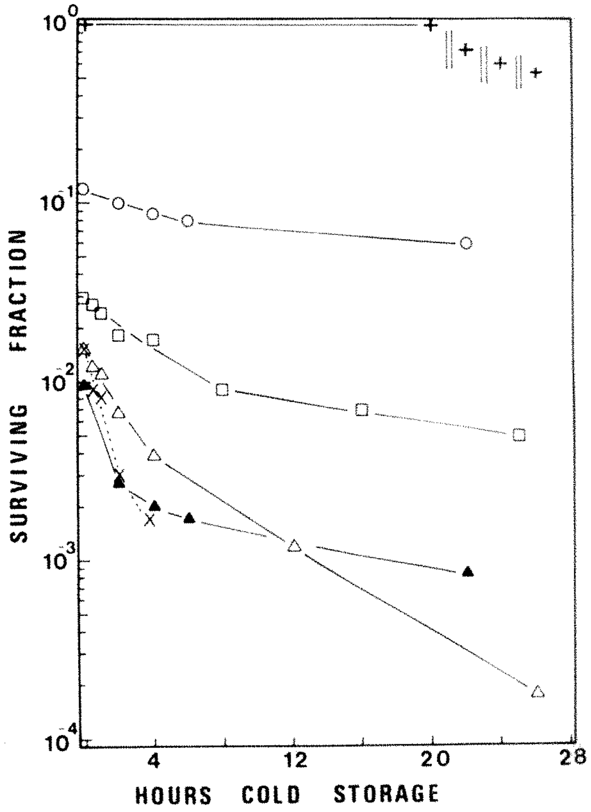

Fig. 1.

The effect of 4°C storage of V79 Chinese hamster cells after irradiation at 4°C (O—800 rad; □—1000 rad; X, △, ▲—1100 rad). Storage in complete medium (O, □, △, ▲) or in phosphate buffered saline (X). There was some scatter in separate experiments done under the same conditions. This may be due to slight temperature differences during irradiation and storage (△, ▲). The survival of unirradiated cells (+) stored at 4°C did not significantly decrease in 30 hours and the last three points represent the survival of these cells after 70, 95 and 115 hours. Standard errors are approximately 10%.

irradiated at room temperature and subsequently stored at 42°C (except that there was almost a 50% decrease in control plating efficiency over 30 hours), in agreement with several recent reports on hyperthermic increases in radiosensitivity (Alfieri *et al.*, 1975; Ben-Hur *et al.*, 1972; Ben-Hur *et al.*, 1974; Love *et al.*, 1970).

In experiments with other cell lines (data not shown), the effect of post-irradiation hypothermia was qualitatively similar, although the magnitude of the sensitization was in some cases smaller. We tested Chinese hamster ovary cells (Harris *et al.*, 1975), HAl cells (Hahn and Little, 1972), and HeLa cells (Painter and Young, 1974) and all showed a synergistic X-ray-cold response. We found that the greatest variation among the responses of the various cell lines was in the initial rapid decrease in survival, with some of the lines showing only the slower component throughout the storage time. Each cell line was grown in its normal medium, usually Eagle's minimal medium with Hank's or Earle's saline buffers.

The cold effect was not related to attachment or medium content since similar results were obtained with the cells in suspension in calcium and glucose-free PBS (Fig. 1). Moreover, it made no difference whether the cells were attached to glass or plastic dishes or whether the cells were growing exponentially or were in plateau phase prior to the experiment. Since CO_2 (or any gas) is more soluble in cold solutions than warm ones, the pH of the medium was slightly less basic at 4°C (7.2 instead of 7.4). However, when the CO_2 concentration in the gas phase of the chambers was reduced from 5% to 2% (which increased the pH back to 7.4) the effect of post-irradiation cold was the same. No changes in pH occurred during storage of the dishes, and we do not believe that the effect is caused by toxic products in the medium, since similar results were obtained if the irradiated medium was replaced by fresh, ice-cold medium immediately after irradiation.

One of the most interesting aspects of the cold effect is that if the cells were warmed to room temperature or 37°C for as little as ten minutes after irradiation, or even if the cells were irradiated at these higher temperatures, no subsequent decrease in survival with storage at 4°C was observed, except for the small changes associated with the unirradiated controls. Since there was no difference in survival for cells irradiated at 0°C or room temperature and then incubated at 37°C, this implies that whatever agent is responsible for the synergistic killing seen in Fig. 1 has a very short half-life at higher temperatures (*e.g.* a rapid repair process may be ineffective at low temperatures).

We have occasionally observed a reduced effect of hypothermia in the first three hours or so after irradiation. Since most other experiments involving X-ray-temperature interactions have only been concerned with short incubation times, the conflicting results in the literature may be due to this initial variation which in turn may be cell-line specific. However, in our hands, hypothermia after X irradiation always caused a decreased survival for long incubation times. Because there was no plateau in the cold-induced X-ray damage potentiation (times as long as four days have been tested), the data point to either an active cellular degradation process, or the continual and irreplaceable loss of the cells' ability to repair X-ray damage. While experiments are presently being done to investigate these possibilities, we feel that the "cold effect" is sufficiently important to report these results in preliminary form. In view of the recent renewed interest in hyperthermic effects with regard to possible tumour therapy (Hahn, 1974), the results reported here may point to the use of any abnormal temperature (*i.e.* higher or lower than 37°C) for the selective killing of X-irradiated cells.

ACKNOWLEDGMENTS

The authors wish to thank Ms. Judy Power for expert technical assistance. Work supported by the United States Energy Research and Development Administration, Contract W7405 eng 48, The Ontario Cancer Treatment and Research Foundation, and the United States National Institutes of Health, Grant CA 14310.

C. J. Koch also wishes to thank the Medical Research Council of Canada for a post-doctoral research fellowship.

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Book review

Urological Radiology of the Adult Male Lower Urinary Tract. Anatomy, Physiology, Pathology and Sequelae—Diagnosis and Management. By R. W. McCallum and V. Colapinto, pp. 358, 1976 (Springfield, Illinois, Charles C. Thomas), $35.50.

The authors are a radiologist and a urologist with considerable experience in this subject, derived from "over one thousand urethrographic examinations during the past seven years". There are seven chapters with the headings: Normal anatomy—Normal radiological anatomy—Anterior urethra—Membranous urethra—Prostate and prostatic urethra—Urinary bladder—Neurogenic bladder. This is therefore a comprehensive text on the adult male urethra, and includes many illustrations and references. It is "aimed at both radiology and urology residents in training, and hopefully, established radiologists and urologists will also find it useful". The book is unexceptionable in this regard, and large libraries will wish to own it. There is just enough surgery and therapy background for the interested radiologist. The authors describe their new technique for examining patients with paraplegia, and I thought this section particularly good.

Thomas Sherwood.

1977, *British Journal of Radiology*, *50*, 294

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

TREATMENT SIMULATORS AND COMPUTER ASSISTED TOMOGRAPHY

The functions of the treatment simulator are localization of tumour volume and verification that the treatment fields include the tumour while sparing healthy tissue. For radiotherapy planning by computer the radiation beams are represented in digital form. We suggest that if accurate and detailed three-dimensional information on the relevant parts of the patient's anatomy, including the positions of reference markers on the skin, is available in digital form as well, it is feasible to verify the coverage of the treatment fields in the patient by computer calculation.

Advances in whole-body computer-assisted tomography (CAT) have led to new capabilities for tumour localization (Chernak *et al.*, 1975). In addition to their advantages for localization, CT scans provide the kind of information required for verification by computer. In this view a CAT scanner, linked to an interactive treatment planning system or with its own radiotherapy programs, can take over both functions of the treatment simulator, so that the treatment simulator as a separate entity is no longer necessary.

In the computerized version of verification, the path of each applied beam in the patient would be demonstrated by means of rays superimposed on the displays of the CAT scans. When needed, three-dimensional isodose distributions corrected for the measured patient contours and inhomogeneities could be calculated.

CAT scanners are expensive and it is hard to justify their purchase by a radiotherapy department for tumour localization alone. However, if one could acquire a radiotherapy oriented CAT system instead of buying separate units for treatment simulation and treatment planning, its price would become more competitive. We are investigating the requirements for the design of such a system, and the validity in practice of replacing the patient by a computer representation for the purpose of verifying radiotherapy fields.

Yours, etc.,
M. TATCHER.

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The North Israel Oncology Center,
Technion-Aba Khoushy School of Medicine,
Haifa, Israel.

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THE EDITOR—SIR,

COSTS AND BENEFITS OF RARE EARTH SCREENS

The cost of introducing rare earth screens into hospitals in the United Kingdom was discussed in the written evidence submitted to the Royal Commission on Environmental Pollution by The British Institute of Radiology (Royal Commission on Environmental Pollution, 1976). It was estimated that the use of these screens would probably reduce the exposure of the population from medical radiography by a factor of two; but at a cost of £1.5m this was not considered to be practical financially at present. Since the annual genetically significant dose to the United Kingdom population from medical radiography is of the order of 10 mrad (Great Britain Parliament, 1960; Matthews and Miller, 1969), a total annual genetic collective dose of nearly 300,000 man-rad would be saved by using rare earth screens. Assuming that a screen lasts about five years, the cost of reducing public exposure in this manner would be about £1 per man-rad.

In view of the public concern over radiation exposure, focused particularly on the nuclear industry, it is worth comparing the above estimate with published assessments of the cost in monetary terms of the risks associated with radiation exposure. Medical irradiation is a special case in that the risk to the individual is considered to be outweighed by the benefit to that individual of undergoing a certain radiological examination. However, medical irradiation also contributes to the genetic dose to the whole population, and some risk will be incurred by future generations rather than the individuals concerned. The costs of reducing the genetic dose from medical radiography can therefore be legitimately compared with the costs of reducing the genetic dose from other sources such as nuclear power wastes. The cost of the detriment associated with genetic collective dose has been assessed as £10 to £30 per man-rad (Dunster and McLean, 1970; Shepherd and Hetherington, 1975) and it is possible that values of at least this order could be applied in a cost-benefit analysis of such topics as the effectiveness of waste treatment in the nuclear industry. For example, the United States Nuclear Regulatory Commission has already specified that a value of $1 000 per man-rad should be incorporated into the design objectives for light water reactors (U.S. Congress, 1976).

It would seem therefore that there is a great discrepancy between the amount of money which the nuclear industry might be expected to spend to reduce public exposure from radioactive wastes and that which it is felt should be spent in the medical field. Surely this situation is rather anomalous?

Yours, etc.,
F. E. TAYLOR.

National Radiological Protection Board,
Harwell, Didcot, Oxon. OX11 0RQ.

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THE EDITOR—SIR,

UPTAKE OF $^{99}Tc^{m}$ COLLOID BY INTRAVASCULAR CLOT

By A. H. Freeman and E. P. Wraight

The above article which appeared in the *British Journal of Radiology*, September 1976, pages 803–804 was read with interest. The superior vena cavagram in Fig. 2 shows multiple filling defects with narrowing of the left innominate vein. There are clots also in the right innominate vein, and the proximal portions of both subclavian veins. But the superior vena cava is well outlined in this figure and I find its obstruction unconvincing.

The ^{99}Tc^{m} uptake in the sternal region is rather too wide for the superior vena cava. You should kindly review the radiograph.

Yours, etc.,
T. M. KOLAWOLE.

Department of Radiology,
University College Hospital,
Ibadan, Nigeria.

THE EDITOR—SIR,

"UPTAKE OF ^{99}Tc^{m} COLLOID BY INTRAVASCULAR CLOT"

With reference to the first paragraph, of the letter from Dr. Kolawole, the problem has arisen because unfortunately the photographic reproduction has not been able to demonstrate the complete details of the original film. The area below the junction of the two innominate veins to which Dr. Kolawole refers as opacified superior vena cava, is, in fact, all due to non-opacified mediastinum, and this is not clearly demonstrated on the photograph. Also, the collateral vessels in that area of the mediastinum have not shown at all on the photograph.

With reference to his second point that the uptake of colloid represents too wide an area for the superior vena cava, it should be noted that the scanner was set up for the peak count rate over the liver. The count rate in the region of the clot was four times as high as this, producing the apparent magnification. A repeat scan, with the correct settings of the clot itself (not included in our communication), gave an image of less than 2 cm width, which is the average size for an adult superior vena cava.

Yours etc.,
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E. P. WRAIGHT.

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THE EDITOR—SIR,

EXPERIENCE WITH THE ALDERSON RANDO PHANTOM

For assessing dose distributions in electron beam therapy of medulloblastoma, thermoluminescent dosimetry with lithium fluoride was our method of choice. As the dose delivered to the spinal cord could be critical and had to be compared with that using other techniques, it was decided to simulate *in vivo* conditions as nearly as possible during measurements. For this the Alderson Rando Phantom (Alderson *et al.*, 1962) of the Radiological Department of the Erasmus University was used. In addition to this, measurements were made in a number of autopsy specimens in order to obtain an idea about the degree of similarity between the phantom and near-*in-vivo* conditions.

Small holes were drilled into the phantom and the autopsy specimens to receive the LiF, and measurements were performed in electron beams of energy 17 MeV, using fields of 8×12 cm^2.

Results

Surprisingly, the measurements in the phantom were much at variance with those in the autopsy specimens. In Table I the results in three specimens from patients aged 6, 11 and 80 years are compared with those in the phantom. The measurements were performed at three locations: two within and one immediately behind the vertebrae. During irradiation, the autopsy specimens were immersed in water.

The table shows the average depths at which measurements were performed (a.d.) together with the depths which give the same attenuation in water, the equivalent depths (e.d.). These results suggest that the density of the bony parts of the phantom is markedly lower than that of the water. Measurements of transmission of X rays in comparison with water phantom measurements confirmed this finding; radiographs of various parts of the phantom, such as Fig. 1A, showed large areas of low density.

TABLE I

COMPARISON OF MEASUREMENTS IN THREE AUTOPSY SPECIMENS AND IN ALDERSON PHANTOM

Age	6 years		11 years		80 years		Alderson Phantom	
Location	a.d.	e.d.	a.d.	e.d.	a.d.	e.d.	a.d.	e.d.
Dorsal side of spinal cord	27	32	29	33	32	42	30	25
Ventral side of spinal cord	38	36	40	40	42	44	42	36
Ventral side of vertebral body	68	68	70	73	78	82	66	55

a.d. = average depth in mm at which measurements were made

e.d. = equivalent depths in mm of water that would produce the same attenuation

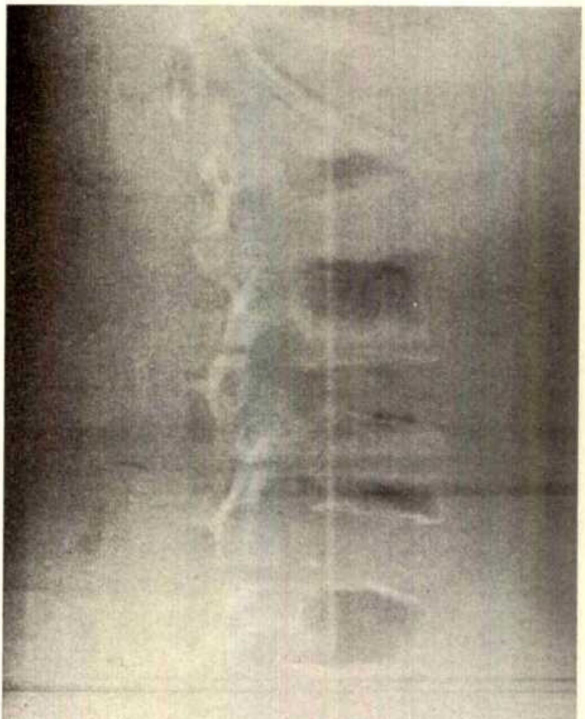
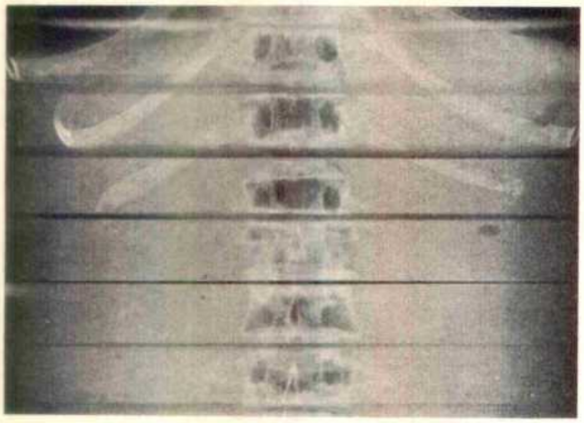


FIG. 1A.



B

FIG. 1.

Radiographs of parts of Rando Phantoms showing areas of low density in vertebrae: (A) Phantom of Erasmus University, Rotterdam; (B) Phantom of The Netherlands Cancer Institute, Amsterdam.

DISCUSSION

Similar experiences have been reported by other users of the Rando Phantom in our country, *viz.* by the Radiological Department of Leyden University and by the Netherlands Cancer Institute (Fig. 1B). The matter was taken up with the manufacturers who stated that, in order to simulate true *in-vivo* conditions, an artificial skeleton would have to be introduced into the tissue-like material of the phantom and that the real skeletons they were using appeared to be unsuitable for electron beam dosimetry. The question remains, therefore, whether when the Alderson Rando Phantom is used in this way, the expense associated with the insertion of these unsatisfactory skeletons into the soft tissue equivalent material is justified.

Yours, etc.,
A. SOMERWIL,
H. J. VAN KLEFFENS.

Physics Department,
Rotterdam Radiotherapeutic Institute,
Rotterdam, The Netherlands.

REFERENCE

ALDERSON, S. W., LANZL, L. H., ROLLINS, M., and SPIRA, J., 1962. An instrumented phantom system for analog computation of treatment plans. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *87*, 185–195.

THE EDITOR—SIR,

THERMOMETRIC-BAROMETRIC CORRECTION FACTOR FOR HUMID AIR

In the National Bureau of Standards (USA) Publication "Design of Free Air Ionization Chambers" (Wyckoff and Attix, 1957), the proposed thermometric-barometric correction factor for humid air is incorrect.

The factor given is (p. 3):

$$\frac{273.2}{T} \times \left(\frac{P—0.238\,P_1}{760}\right)$$

The correct factor is:

$$\frac{273.2}{T} \times \left(\frac{P—0.3783\,P_1}{760}\right)$$

where P_1 is the partial pressure of H_2O in mm of mercury.

Wyckoff and Attix quote the *Handbook of Chemistry and Physics*, 1954–1955, 36th Edition, p. 1965, as the source of the factor 0.238 P_1. In that issue and all subsequent issues through the current (56th Edition, p. F9) the value is determined to be 0.3783 P_1.

Experimentally the deviation from the correct value introduced by using the incorrect correction factor is probably below detection, because it is a second order correction factor. Unfortunately it is already in the textbooks (Johns and Cunningham, 1969).

Yours, etc.,
E. S. WHEELER

Physics Department,
The University of Texas System Cancer Center.
Texas Medical Centre,
Houston,
Texas 77025, U.S.A.

REFERENCES

Handbook of Chemistry and Physics, 36th Edition, 1954–1955, p. 1965–1969.

Handbook of Chemistry and Physics, 56th Edition, 1975–1976, p. F9.

JOHNS, H. E., and CUNNINGHAM, J. R., 1969. *The Physics of Radiology*, 3rd Edition, p. 208.

WYCKOFF, H. O. and ATTIX, F. H., 1957. Design of Free Air Ionization Chambers. *National Bureau of Standards Handbook*, *64*, 3.

THE EDITOR—SIR,

SI PREFIXES

In response to the letter in the August issue of *The British Journal of Radiology* by Dr. Pfalzner regarding SI prefixes, I respectfully suggest that his suggestions, while indeed possessing logical consistency, embody a system that could prove burdensome and confusing. Certainly one would need his Table II at hand for a long time until it was all memorized. I propose that prefixes could be eliminated entirely by using the following notation for the size of a quantity:

$A\,E\pm MN$ (units),

where $0 \leqslant A < 1$, and M and N are integers from zero to 9, and (units) is the symbol for the unit in question, *e.g.*, J (for (Joule).

For example,

"0.130 E+ 05 Bq" would be interpreted as meaning, "$0.130\times10^{+5}$ Bq"

This notation has several advantages: (1) The power of 10 involved is instantly apparent. (2) No prefixes need be memorized or looked up. (3) Typing and typesetting can all be done on one line (no superscripts for the exponent). (4) This notation is already familiar as "scientific notation" in computing circles.

With regard to expressing the quantity verbally, would it be more difficult to say "zero point one three zero times ten to the plus five Bequerel" than "thirteen point zero Tri-pos Bequerel"?

As a slight variation it could be agreed upon that in the symbolic formula, $1 \leqslant A < 10$, but the quantity would be clearly understandable either way. Also the plus signs could be left off for positive numbers.

Yours, etc.,
A. FELDMAN.

Radiology Department,
The Methodist Medical Center of Illinois,
Peoria, Illinois 61636, U.S.A.

REFERENCE

PFALZNER, P. M., 1976. A proposal for SI Prefixes. *British Journal of Radiology*, *49*, 739.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

B.I.R. LIBRARY

The opening of the Institute's house for members to use the Library on Saturday mornings has been discontinued through lack of support. However, arrangements would be made for the Library to be opened between 10.00 a.m. and 1.00 p.m. on a Saturday if prior notice was given. Telephone 01–935 6237 or write to The General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

THE BRITISH INSTITUTE OF RADIOLOGY ANNUAL CONGRESS AND SCIENTIFIC EXHIBITION

To be held on April 14–15, 1977 at the R.I.B.A., 66 Portland Place, London W1. Papers presented will include the "Silvanus Thompson Memorial Lecture" entitled *The present state of computed tomography and its future*, by Mr. G. N. Hounsfield, C.B.E., of EMI Central Research Laboratories.

Further information and registration from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

RADIATION PROTECTION: AN EXAMPLE OF ACTION AGAINST MODERN HAZARDS

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P., no. 33, 92260 Fontenay-aux-Roses, France.

THE MACKENZIE DAVIDSON MEMORIAL LECTURE

To be given by Dr. David Ingvar, University of Lund on May 19, 1977 at The British Institute of Radiology. Functional landscapes in the brain studied with regional blood flow measurements.

NEW HORIZONS IN INTENSIFYING SCREEN TECHNOLOGY

An all-day meeting organized by the Industry Committee of The British Institute of Radiology on May 20, 1977 at the Middlesex Hospital Medical School, London, W1. Registration details and information from the General Secretary, The British Institute of Radiology.

RECOVERY AND REPAIR

A work-in-progress meeting organized by the Radiology Committee of the British Institute of Radiology will be held at the Institute House on Friday May 20, 1977. Further information from the General Secretary, 32 Welbeck Street, London W1M 7PG.

EXPERIMENTAL AND CLINICAL APPLICATIONS OF KRYPTON 81M

An all-day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology to be held at the Middlesex Hospital Medical School, London, W1 on June 3, 1977. Registration and details from the General Secretary.

PROGRESS IN EXPERIMENTAL RADIOTHERAPY

A meeting organized by the Netherlands Radiobiological Society in collaboration with the B.I.R. will be held on June 6–7, 1977 in Essex.

Subjects will include neutron radiobiology and radiotherapy, hypoxic cell sensitizers, chemotherapy and combined modalities.

Further details can be obtained from J. J. Broerse, Radiobiological Institute TNO, Lange Kleiweg 151 Rijswijk, The Netherlands, or S. B. Field, MRC Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12 0HS.

HYPOXIC CELL SENSITIZERS IN RADIOBIOLOGY AND RADIOTHERAPY

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

SIXTH INTERNATIONAL CONFERENCE ON THE USE OF COMPUTERS IN RADIATION THERAPY

Will be held at Gottingen on September 18–23, 1977. Further information from: R. E. Bentley, Physics Department, Royal Marsden Hospital, Downs Road, Sutton, Surrey, or Professor U. Rosenow, Strahlenabteilung, Unit.-Frauenklinik, D-34 Gottingen, Fed. Rep. Germany.

XIV INTERNATIONAL CONGRESS OF RADIOLOGY

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV International Congress of Radiology, Avenida Churchill 97—5th Floor, ZC 39, 20,000, Rio de Janeiro, Brazil.

TUMOUR ULTRASOUND '77

An international symposium on the science and clinical practice of ultrasound diagnosis and localization of tumours will be held in London, on December 5–6, 1977. This has been arranged in conjunction with the Annual Scientific Meeting of the British Medical Ultrasonics Group which will be held on December 7–8, 1977 at the same venue. A commercial and scientific exhibition will be held throughout both meetings. It is intended that the meeting will give a systematic coverage of the field and that the published proceedings will provide an up to date view of the subject. For registration and abstract forms or further details write to Dr. Ralph McCready, Department of Nuclear Medicine and Ultrasound, Royal Marsden Hospital, Downs Road, Sutton, Surrey, U.K.

Book reviews

Introductory Medical Statistics. By R. F. Mould, pp. xi+98, 1976 (Tunbridge Wells, Kent, Pitman Medical Publishing Co. Ltd), £4·00.

Ever since medical statistics were introduced into the syllabus of the F.R.C.R. (Radiotherapy) Part I, it has been a problem to know what text-book to recommend to candidates for the examination. Many existing statistical textbooks only put off the candidate by spreading before him far more knowledge than he needs, often with much frightening mathematics, and with practical examples that are seldom drawn from the field of oncology. It is therefore with great interest and hope that one opens this book, written by a physicist with considerable experience both in radiotherapy and in medical statistics, and one is not disappointed.

It must be stated straight away that the book is aimed, quite rightly, at a wider readership than the candidates for the F.R.C.R. It is commendably short with an attractive layout and a high proportion of diagrams to text. In some places its conciseness might make it a little difficult for the reader with no previous knowledge at all of statistical ideas but, in general, it should be well within the comprehension of an F.R.C.R. candidate, who will find particularly relevant the last two chapters on the calculation of survival rates and and on clinical trials. Earlier in the book one might have wished for a little more discussion on the concept of sampling as a means of deducing the characteristics of a population. The formula given for the standard deviation in a context in which the author appears to be talking about a sample is, in fact, the formula for the estimate of the standard deviation of the population from which the sample is drawn.

Regrettably there are a number of other errors which it is to be hoped will be corrected in a second edition. In a histogram the *area* and not the *height* of each block should be proportional to the numbers in the intervals particularly when the intervals are unequal as in the example given. In testing for significance in a binomial problem (Tables 5.4 and 5.5) one should not just take the probability of occurrence of the observed sample, but should add on to this the probability of occurrence of more extreme samples.

The calculation of χ^2 for a 2×2 contingency table is very clearly set out, but some mention should have been made of the advisability of using Yates' correction, particularly when the numbers are small. A diagram showing two curves resulting from a trial (Fig. 6.4) is followed by the statement "If, for a single X-value, the 2σ error bars overlap, then this indicates that there is no significant difference . . . for that particular X-value". This is misleading, as overlapping confidence limits can still be consistent with a significant difference at the $P=0.05$ level. Although the author then states rightly that "judging error bars by eye is no substitute for testing the null hypothesis . . . using the formal tests of significance", the problems involved in testing for differences between survival curves are not really dealt with. One hesitates to ask for more mathematics, but if formulæ are given for the standard errors of the constants of a regression line, then would it not also have been useful, in the context of survival curves, to give the formula for calculating the standard error of a survival rate calculated by the life-table method? The logrank test for comparing survival curves could also have been mentioned, even if only to make the student aware of its existence, since he is likely now to see this test frequently quoted in the literature of clinical trials.

These minor criticisms do not, however, detract from the value of this book as a very readable introduction to medical statistics, and one which should help many F.R.C.R. candidates to an easier grasp of the basic statistical ideas that they require for their future practice of radiotherapy and oncology.

J. L. HAYBITTLE.

Scintillation Camera Lung Imaging. An anatomic atlas and guide. By Charles H. Mandell, pp. 19, Illus., 1976 (New York, Grune & Stratton Inc), $28.00.

For most people, lung images are amongst the most difficult to interpret. This atlas will be extremely useful in making lung scintigram interpretation easier.

In the first few pages there are brief comments on anatomy, physiology, radiopharmaceuticals and instruments. The following section is devoted to a series of images illustrating the defect which would be produced by an embolism to each lung segment. Each image is accompanied by a line diagram. These scintigrams have been carried on a lung model in which the appropriate segment can be removed. The illustrations are extremely clear and prove the value of the recommended posterior oblique views. The clinical cases are not quite so clear but do illustrate typical lung perfusion patterns in a wide variety of diseases. There are a few xenon studies but, of course, the high quality pictures now possible with krypton 81m have not had time to reach this type of book.

In summary this is a valuable reference book especially for the reporting room.

RALPH MCCREADY.

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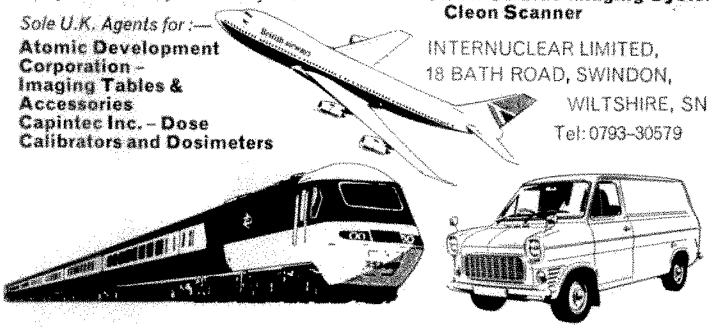

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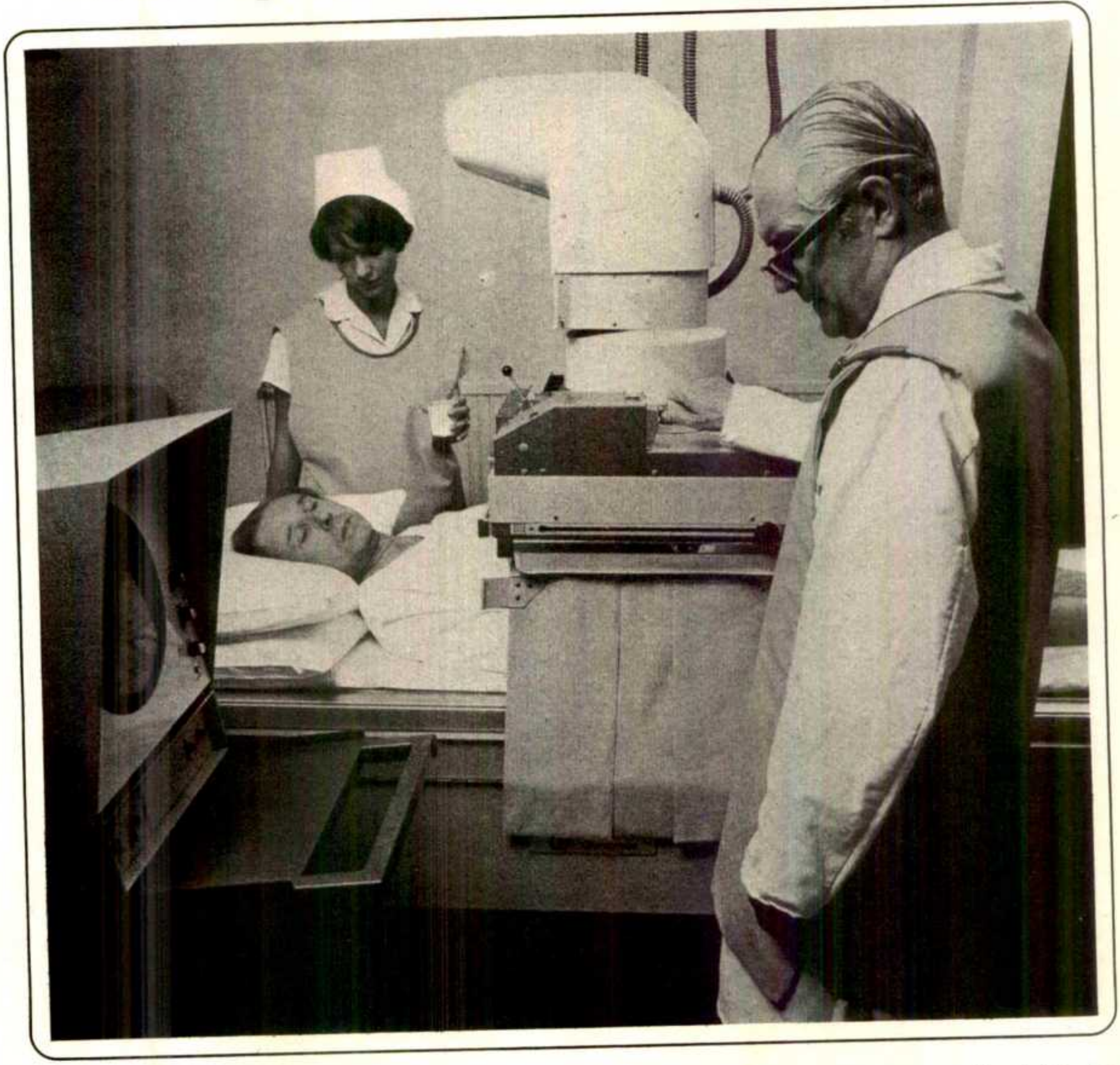

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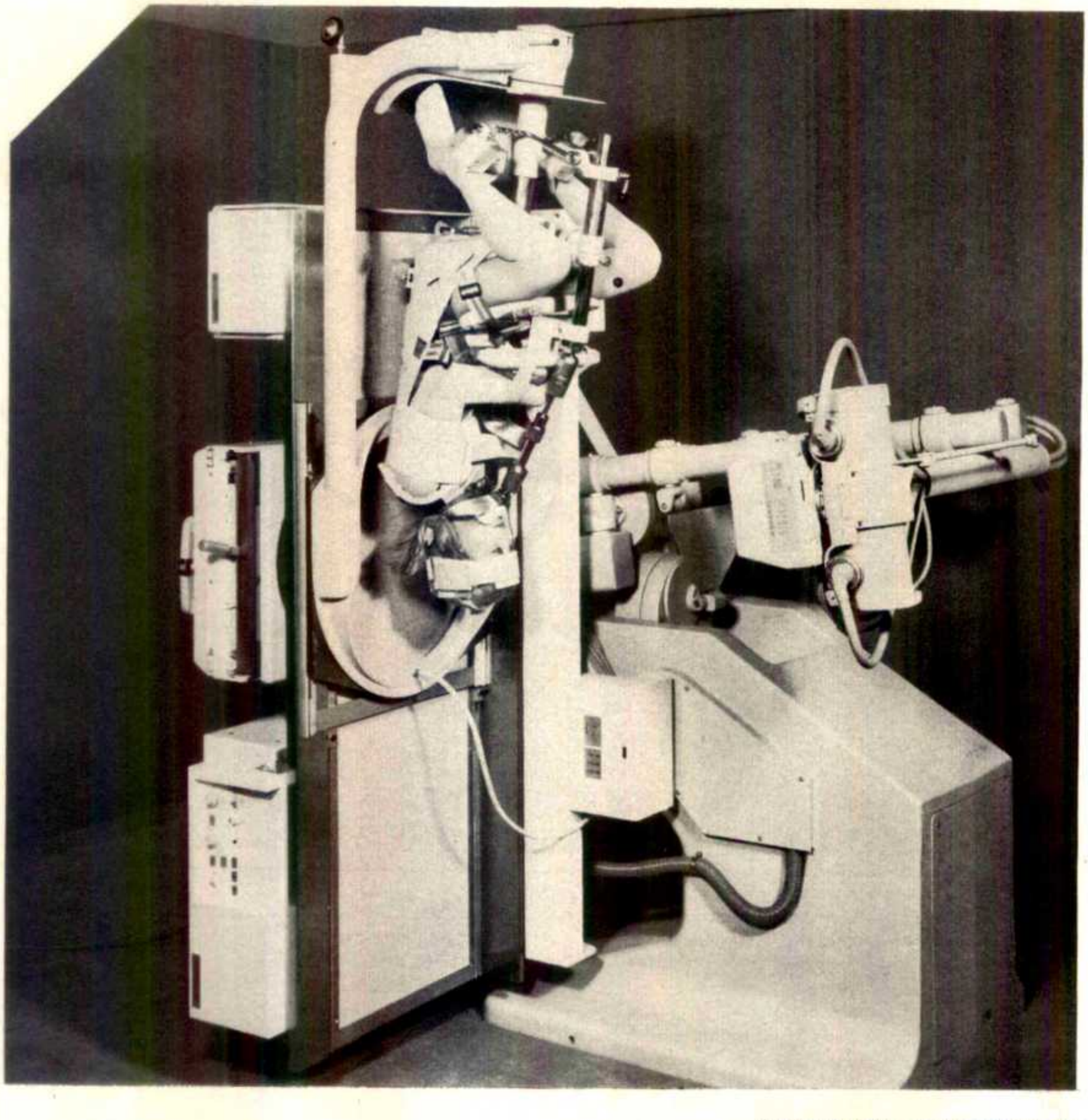
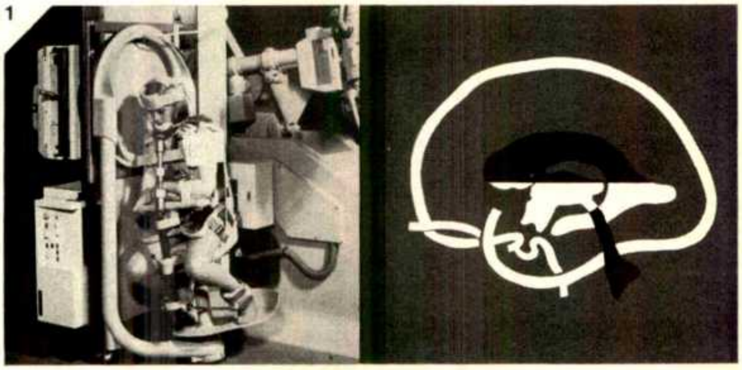


A stage in filling the temporal horns

and Pneumo Chair

Isocentric patient positioning keeps the patient's head in the fulcrum for all projections. And POLYTOME and chair are fully synchronized for proper filling of ventricles and temporal horns. Compact, lightweight easily and quickly attached, dismounted and stored in the POLYTOME room, the new chair gives you full use of all the POLYTOME capabilities: from linear to the famous hypocycloidal blurring motions . . . layer height adjustment . . . superb image quality every exposure . . . constant enlargement for every layer . . . optimum visibility of the patient throughout the examination. Add a Pneumo Chair to any new or existing POLYTOME for a dedicated neuroradiological system. Detach the chair and return the POLYTOME to its role as top department performer !

1



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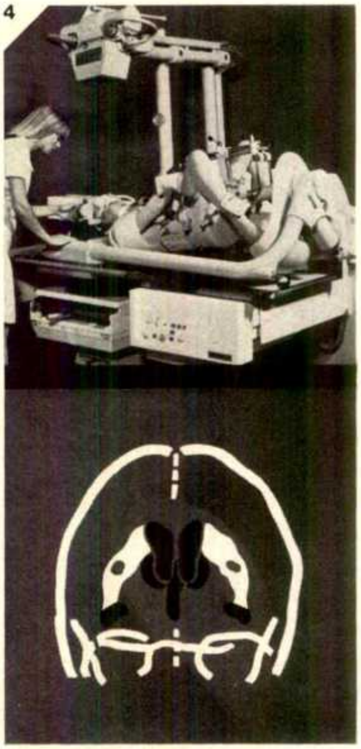

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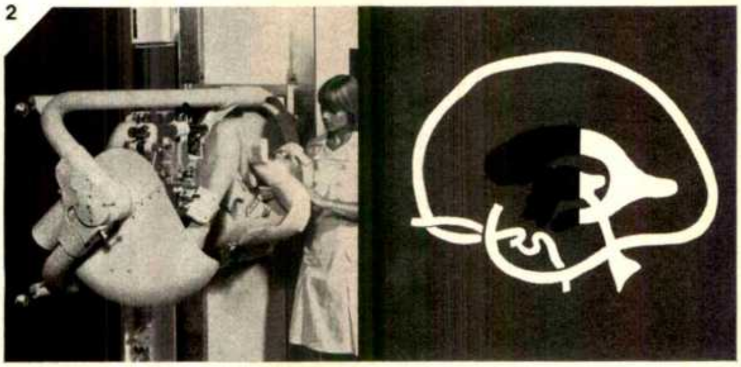

3

Selected patient positions and visualizations in a common pneumo procedure

1. Erect: lateral
2. Brow-up: lateral
3. Brow-down: PA
4. Brow-up: AP

(After sequential filling of temporal horns)

For further details contact
Philips Medical Systems,
Eindhoven, The Netherlands.
or
Philips Medical Systems Ltd.,
45 Nightingale Lane,
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A permanent appointment will only be offered to a radiologist more than two years post qualification. Less experienced radiologists may be offered a one or two year appointment.

Further information on conditions of service, provisions of travel expenses and details of the hospital and the department are available on request from the Head of the department. Applications close 31st May, 1977, and should be forwarded together with the names and addresses of three referees, a recent photograph and curriculum vitae, to—

The Medical Superintendent,

SIR CHARLES GAIRDNER HOSPITAL,

Perth Medical Centre, Nedlands, Western Australia 6009.

XI SYMPOSIUM NEURORADIOLOGICUM

June 4–10, 1978
in Wiesbaden

Themes:

1 Paediatric neuroradiology

2 Neuroradiology of vascular and atrophic lesions in the geriatric age

3 Neuroradiological therapy (i.e. catheterisation and superselective angiography with embolisation of intra- and extracranial lesions and lesions of the spinal cord)

4 Comparison of computerised tomography with other neuroradiological examination methods

Information:
Prof. Dr. S. Wende,
Department of Neuroradiology,
University Hospital,
Langenbeckstrasse 1,
6500 Mainz (FRG)

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On 7th July 1977, at Edward Lewis Lecture Theatre, The Middlesex Hospital Medical School.

Topics to include:

Development of C.A.T.
'C.A.T.' Anatomy
Practical Experience
Therapy Applications
Diagnostic Applications

The Symposium commences at 9.30 a.m., closes at 4.00 p.m. The fee inclusive of lunch, etc., is £10. Cheques, payable to London Borough of Ealing, should be sent **(by June 10, 1977 at latest)** to Accounts Office for the attention of M. Grimshaw, Symposium Organizer, Acton Technical College, High Street, London W3 6RD. Tel. 01–993 2344, ext. 2129.

SPECIAL SUMMER PROGRAMS AT M.I.T.

PRINCIPLES OF NUCLEAR MEDICINE 18–22 JULY 1977

This Program will deal with the state of the art in nuclear medicine with emphasis on physical aspects. Topics to be covered include instrumentation, radiopharmaceuticals, dosimetry, and data processing as well as specific organ studies and therapy.

PRINCIPLES OF COMPUTERIZED TOMOGRAPHY, 25–29 JULY 1977

This Program will deal with the state of the art in computerized axial tomography with emphasis on physical aspects. Topics to be covered include the physics of radiation interaction with biological tissues, instrumentation, algorithm development and computer systems for image reconstruction, the use of contrast agents, artifacts—cause and cure, and specialized areas of imaging.
The Programs should be of value to both physicians and physical scientists working in the areas. They are jointly sponsored by the Harvard Medical School and M.I.T. through the Harvard–M.I.T. Program in Health Sciences and Technology. For further information write to: Director of Summer Session, Room E19–356, M.I.T., Cambridge, Ma. 02139.

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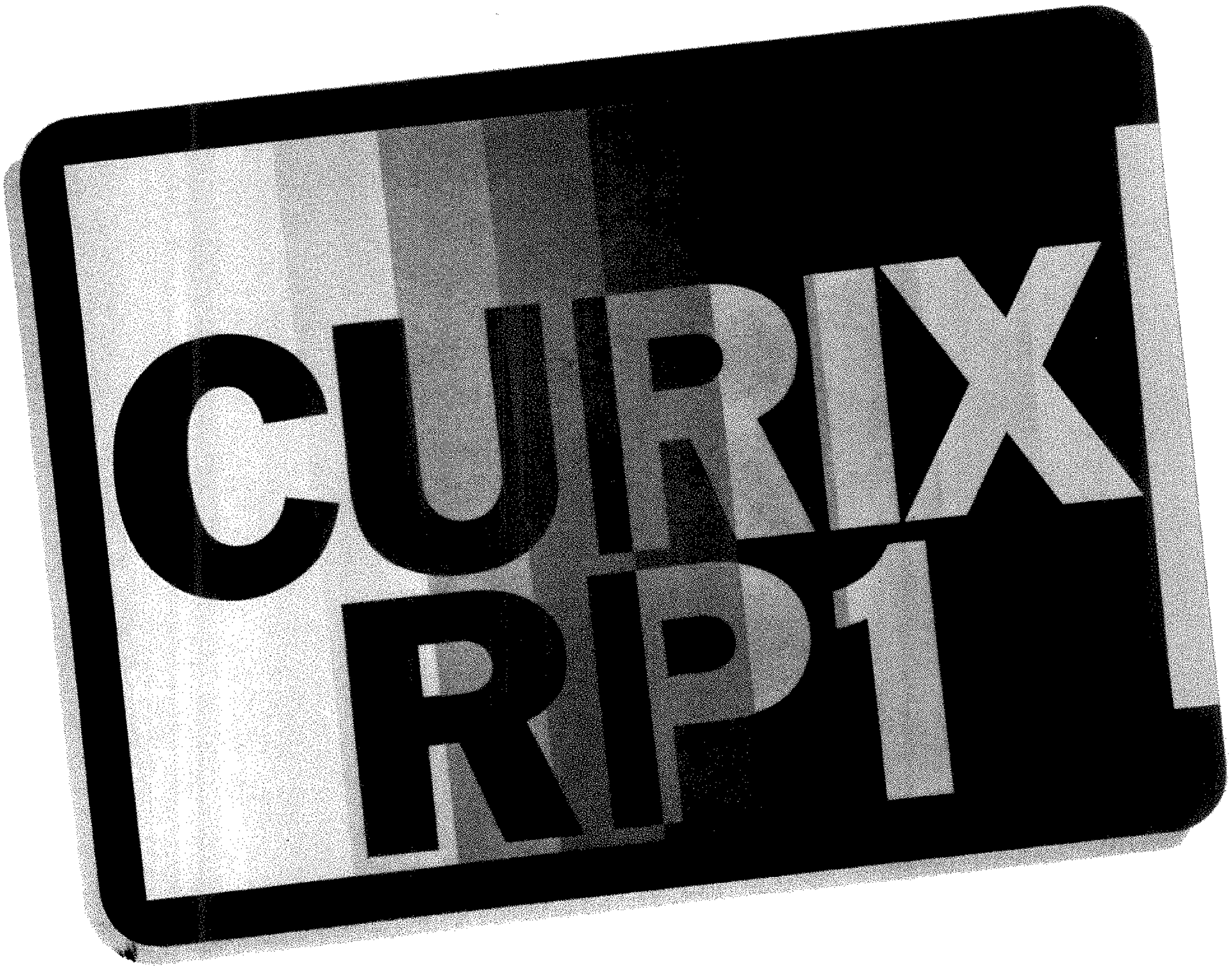

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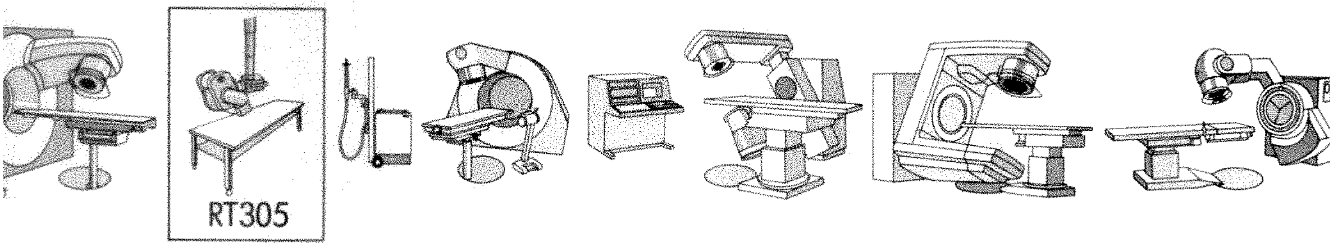

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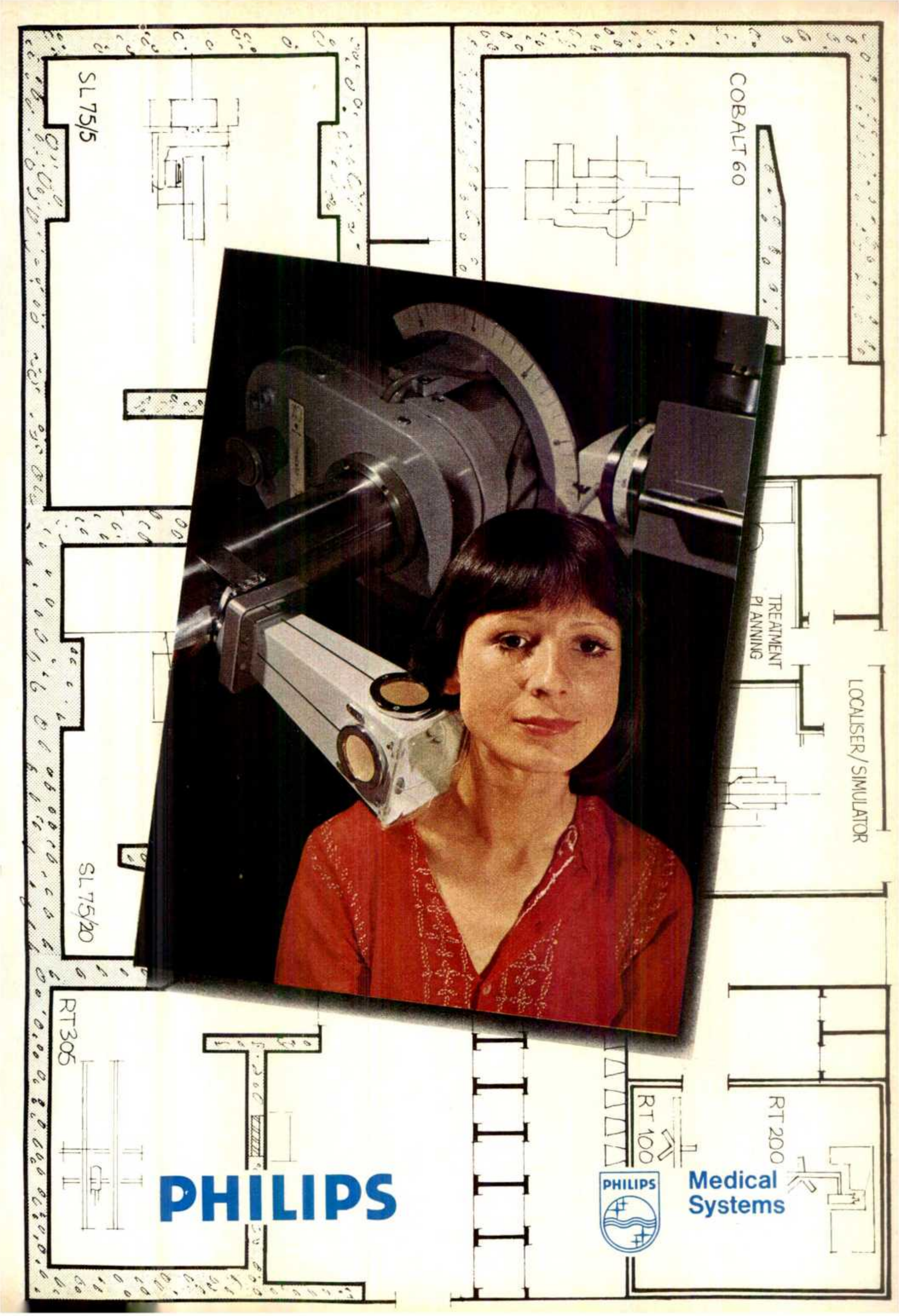

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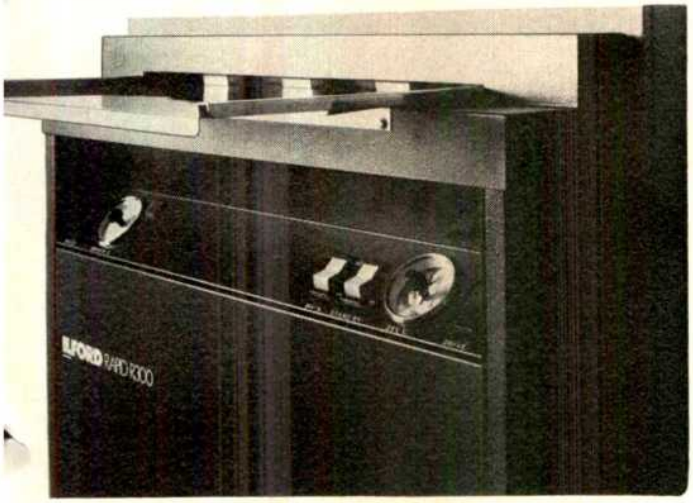

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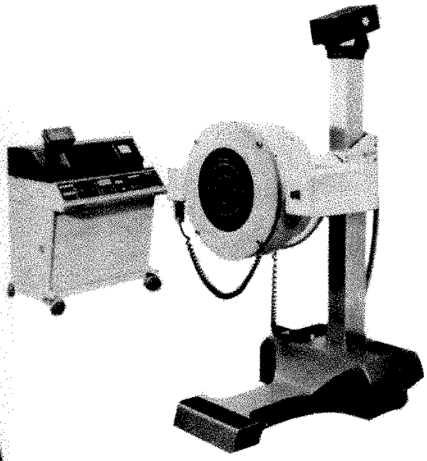

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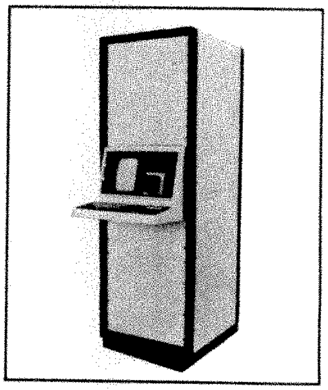

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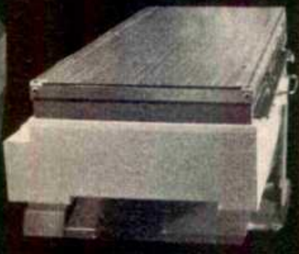
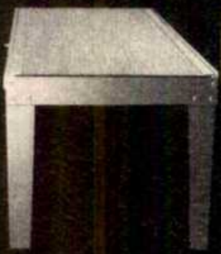
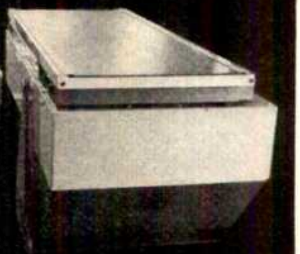


Sparta Tilting Bucky Table— motorised tilt for easy examination of standing and recumbent patients.



Horizontal Bucky Table— full length traverse Bucky unit beneath table.



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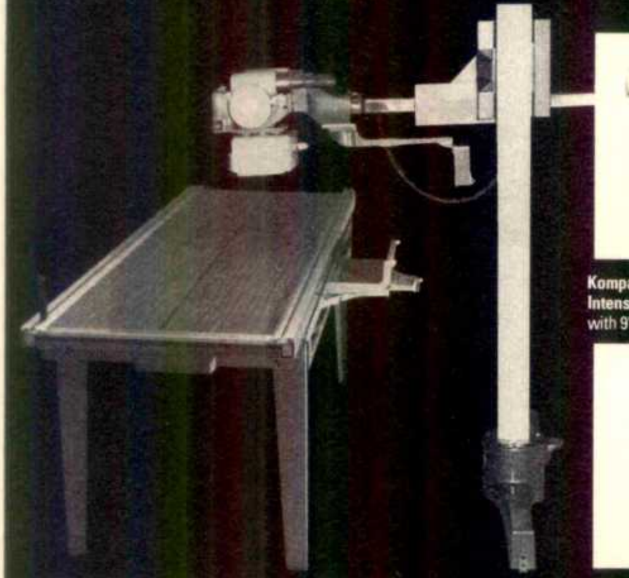

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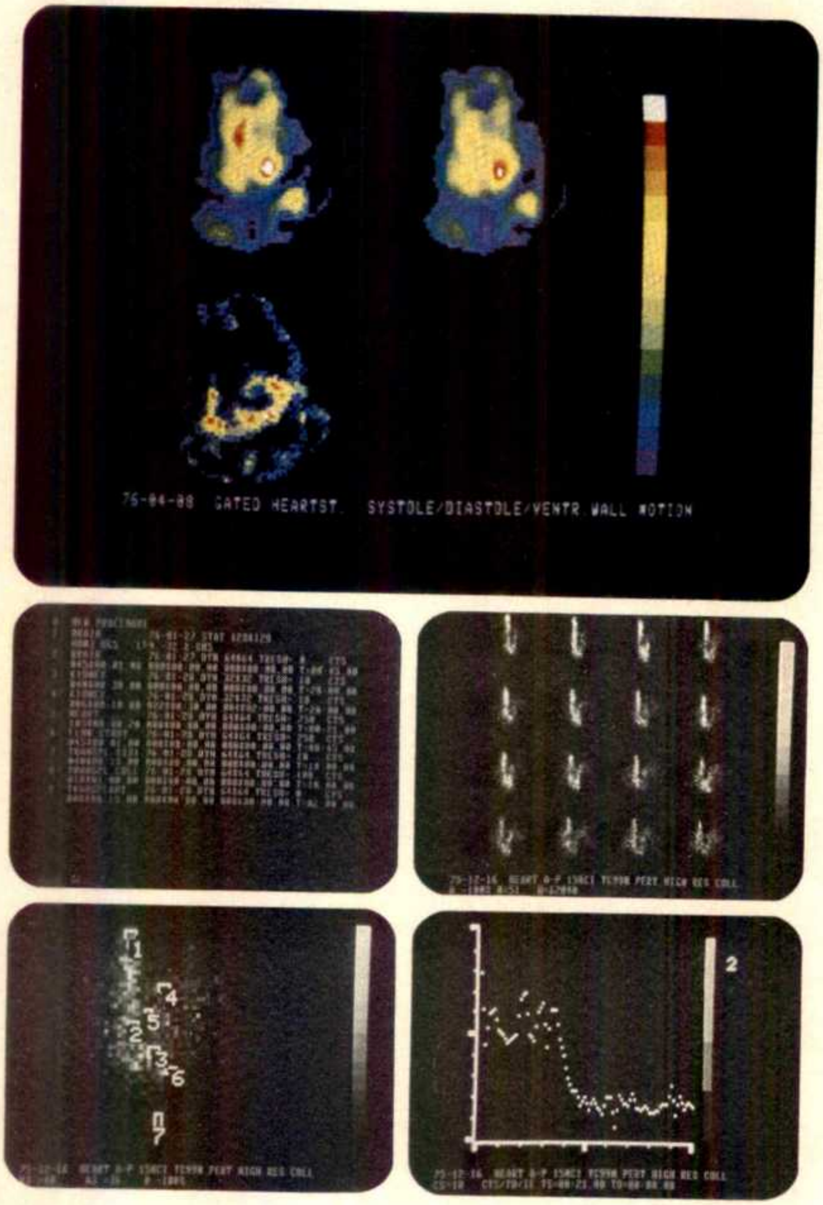

PHILIPS Medical
Systems

Modern radio-isotope techniques enable non-invasive vizualisation of ischemic areas of the heart . . . and processing the mass of data obtained is a task for a Philips Processing and Display System. In the colour video display, the two upper images show the heart in systole and diastole, acquired under ECG gating, while the third image, corresponding with the motion of the ventricular wall, is generated by a special program. If desired the user can also compose special programs – by simply linking existing sub-routines – and call them at any time by pressing the relevant program number.

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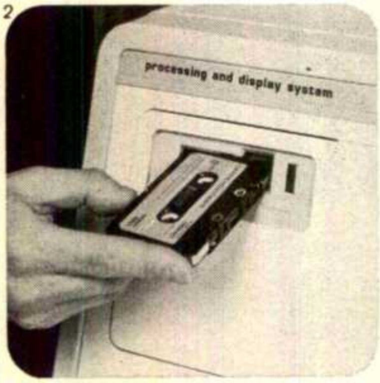
This indepth evidence admirably illustrates the effectiveness of the Philips Processing and Display System in providing rapid quantitative and qualitative diagnostic information obtained during dynamic investigation in nuclear medicine.

The system employs a Philips mini-computer with a 32k 16-bit memory which, together with disc-operated software programs, provides considerable processing speed and flexibility. Furthermore, it has been designed specifically for use by medical personnel and program execution requires no specialized knowledge of data processing techniques.

1

2



3

1 **Direct access** to disc-stored programs covering a complete range of routine examinations is by means of ergonomically grouped key arrangements; the results being immediately displayed on the 30 cm black-and-white video monitor. The system can be extended with a colour monitor. Frequently used procedures can be combined to form new programs. In cases where a single key offers the choice of more than one routine, the program assumes a 'question-answer' mode enabling the operator to make a suitable choice. Incorrect operation is not possible. If a non-acceptable procedure is inadvertantly selected, the keyboard is immediately blocked and an 'error' condition displayed on the monitor.

2 **Software programs,** including standard as well as improved routines, are introduced via the system's built-in compact-cassette recorder. This facility also enables results to be recorded for eventual image playback and appraisal.

3 **FORTRAN IV option.** The capability of Philips Processing and Display System can also be extended to solve special problems. In such cases data can be pre-processed in the convenient PDS way and further analysis carried out using the FORTRAN IV option. Programs can be written in FORTRAN language by the user and results monitored on the PDS display or printed-out on the same terminal that is used to enter or retrieve the FORTRAN program.

Part of a complete program of nuclear medicine equipment and systems, and fully supported by an international service organisation, the Philips Processing and Display System represents the perfect integration of operational simplicity and efficiency with applicational flexibility and reliability.

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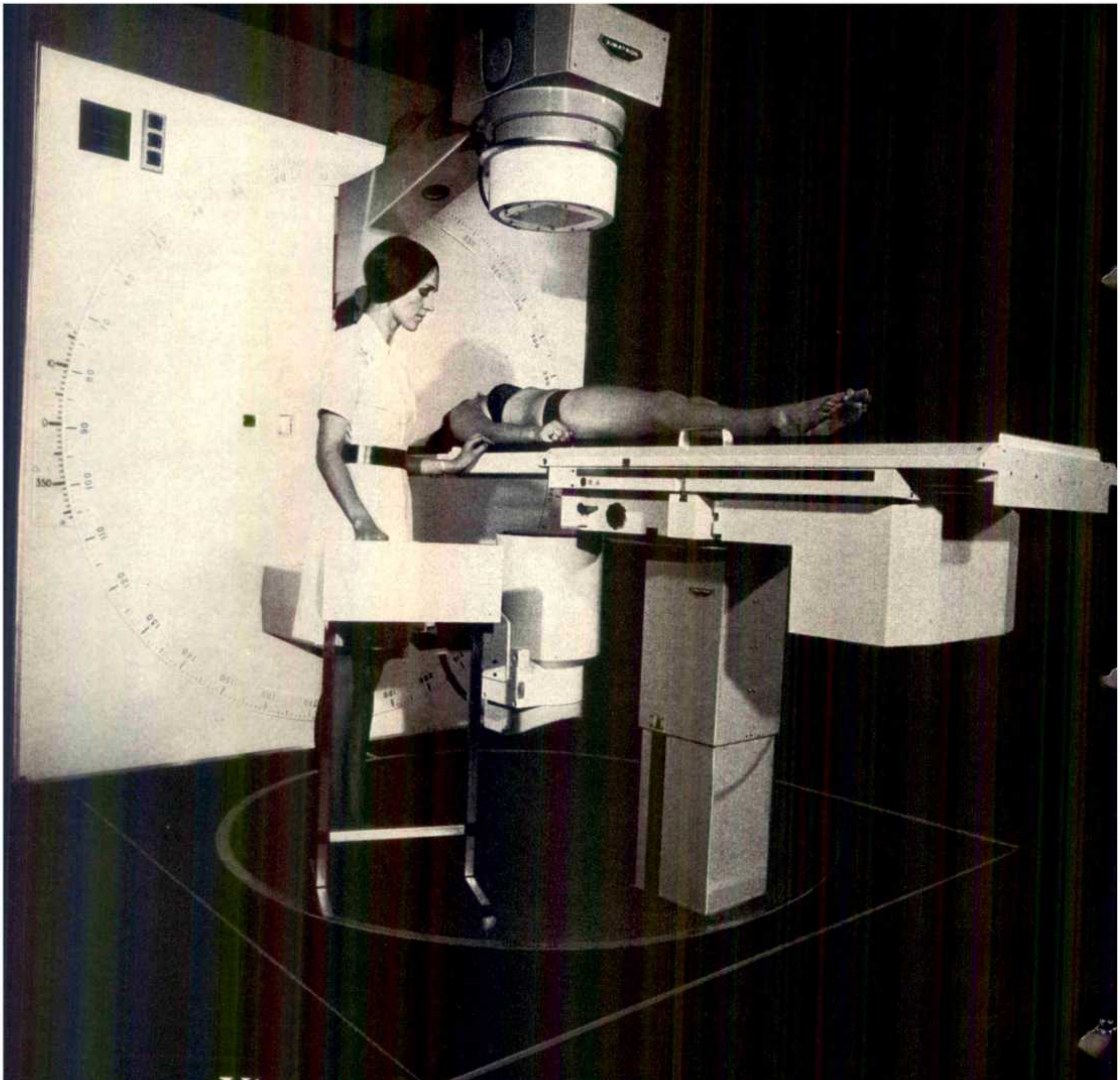

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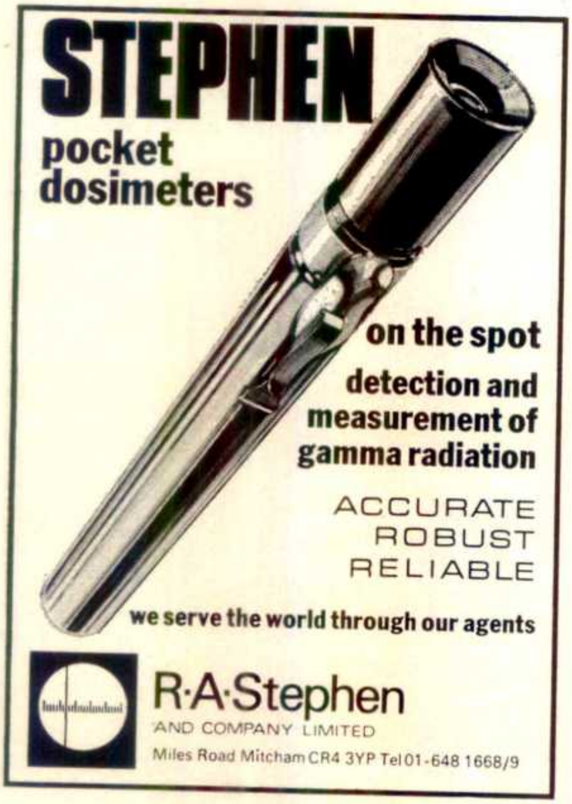

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THURSDAY 26th MAY 1977

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Course fee: £8. Applications as soon as possible but not later than Monday 23rd May 1977.

Speakers will include

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Dr. T. Sherwood, Institute of Urology
Professor Stuart Campbell, King's College Hospital
Dr. H. Meire, Clinical Research Centre
Mr. N. Addison and Dr. O. J. Follows, Bradford Royal Infirmary
Dr. F. G. M. Ross, Bristol Royal Infirmary
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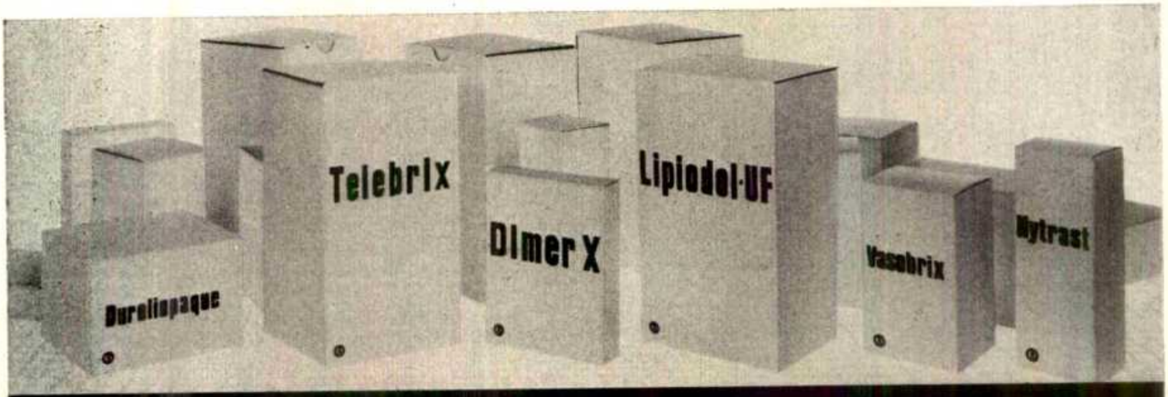

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The four-year programme provides a wide range of training in all aspects of radiation oncology and allied disciplines leading to the Fellowship of The Royal College of Physicians (Canada).

Previous accredited training may be taken into account and applicants with a minimum of one year of internal medicine experience will be given preference.

Applications, with *curriculum vitae* and names and addresses of three referees, should be submitted to **Dr. S. M. Jackson, Programme Director for Residency Training in Radiation Oncology, Cancer Control Agency of British Columbia, 2656 Heather Street, Vancouver V5Z 3J3, Canada, by July 31, 1977.**

Radiation Oncology Department, Michael Reese Hospital and Medical Center, Chicago, Illinois

Applications are invited for a staff position in Radiation Oncology. Minimum qualifications are three years of specialty training, board certification (or eligibility) in Radiology (Therapeutic) and an interest in clinical or basic research. The successful candidate will have responsibility in research and clinical programs, and the teaching of residents and will be encouraged to engage in independant research. The Radiation Oncology Department has ongoing clinical, education and research programs and there is active encouragement and support for new areas of research. Equipment includes megavoltage photon and electron beam therapy, brachytherapy (including ^{125}Iodine) medical physics, computation, radiobiology and animal laboratory facilities. Membership in national co-operative clinical trial groups (N.S.A.B.P. and R.T.O.G.) participation in the Fermilab Neutron Therapy Program and other research projects provide a stimulating environment which will enable the applicant to learn research techniques and to develop new projects. The level of Academic appointment at the University of Chicago and remuneration will depend on the background and experience of the candidate.

Send curriculum vitae and autobiographical letter to Lionel Cohen, M.D., Ph.D., Chairman, Radiation Oncology Department, Michael Reese Hospital and Medical Center, 29th Street and Ellis Avenue, Chicago, Illinois 60616.

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A limited number of staff appointments are available in Radiation Oncology at the Cancer Control Agency of British Columbia. Successful applicants will be involved in the development of an expanding facility within a multi-disciplinary cancer clinic offering ample academic opportunities.

Applicants with higher qualifications in radiation oncology and/or allied disciplines will be given preference. Applicants must be eligible for registration in British Columbia and hold, or be eligible to sit, the F.R.C.P.(C) examinations. Salary scales are competitive and available on application.

Applications, together with *curriculum vitae* and names and addresses of three referees, should be sent to **Dr. S. M. Jackson, Head of Radiation Oncology, Cancer Control Agency of British Columbia, 2656 Heather Street, Vancouver V5Z 3J3, Canada.**
Closing date for applications June 30, 1977.

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Diplomate of American Board of Radiology, or eligible for examination, with one to two years' training in Pediatric Radiology in a recognized center. Full time pediatric diagnostic roentgenology, including service, teaching, and research or clinical investigation. Opportunities for special procedures and ultrasound. Post carries an appointment in the Departments of Radiology and Pediatrics, University of Cincinnati.

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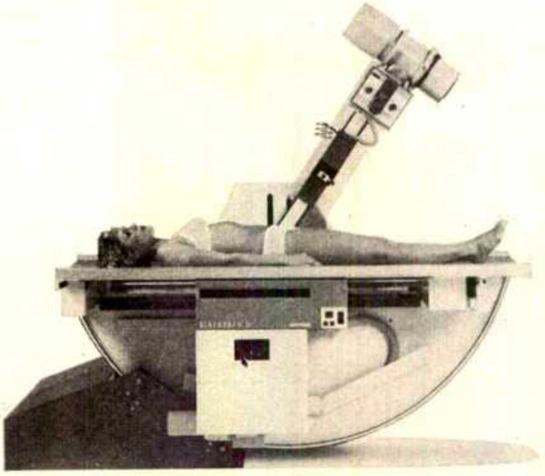

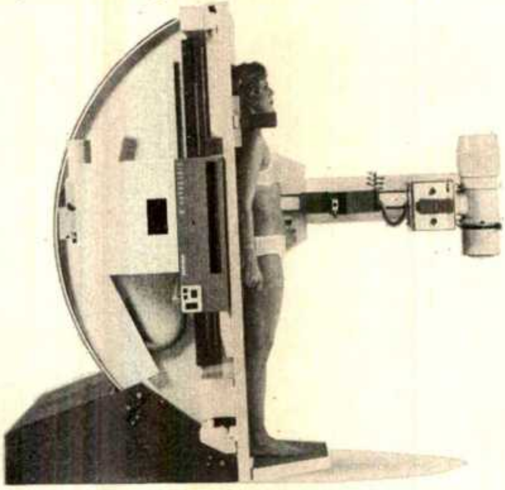

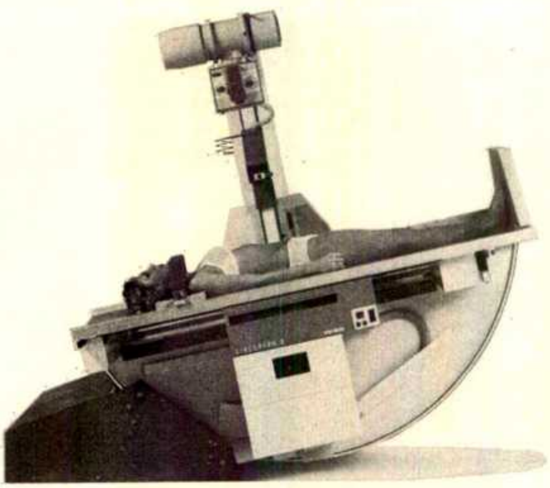

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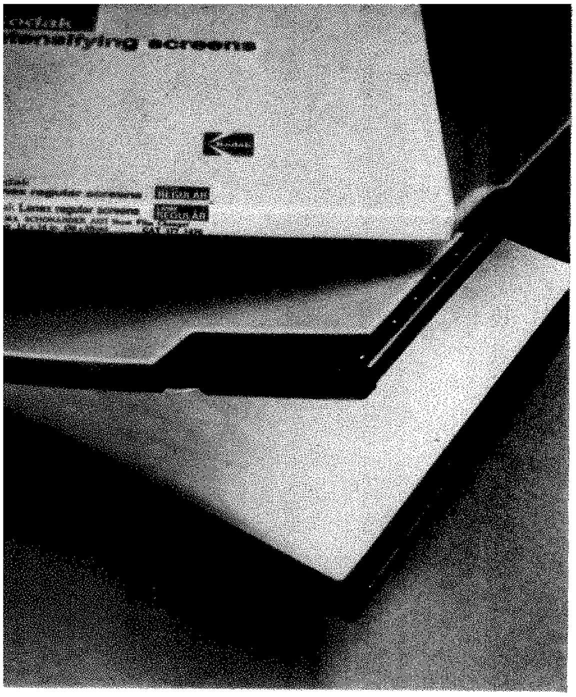

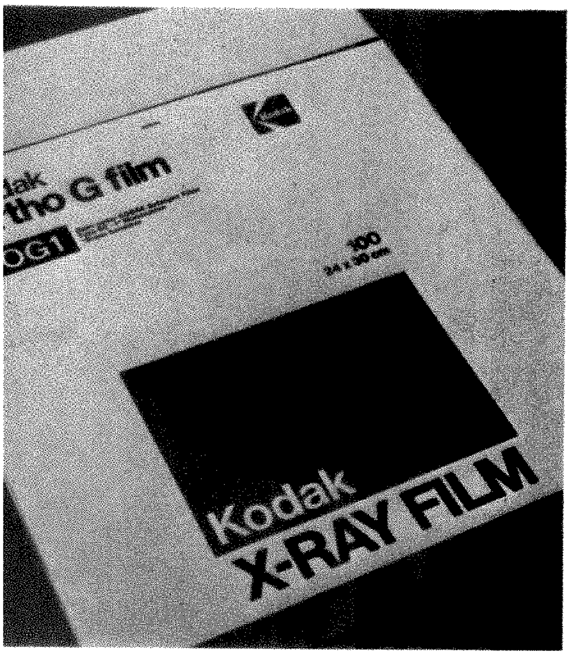

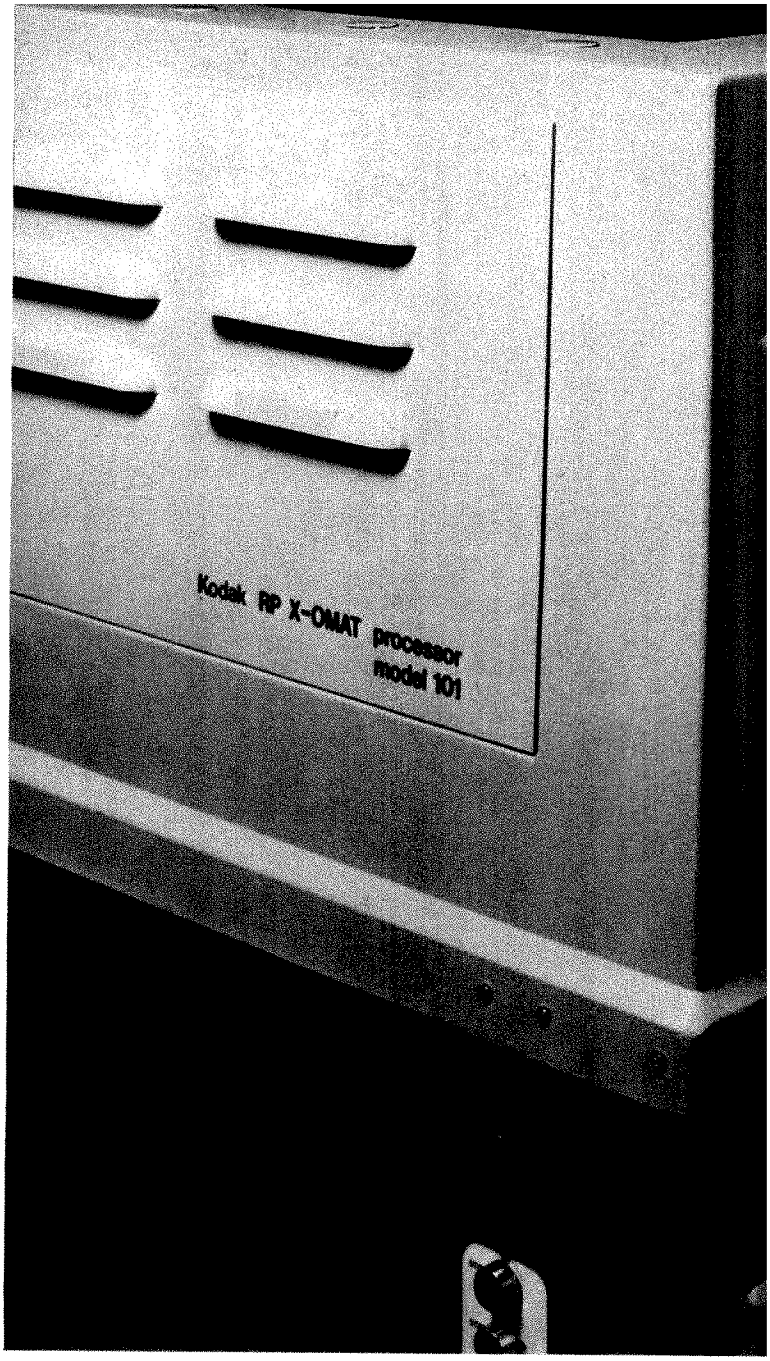

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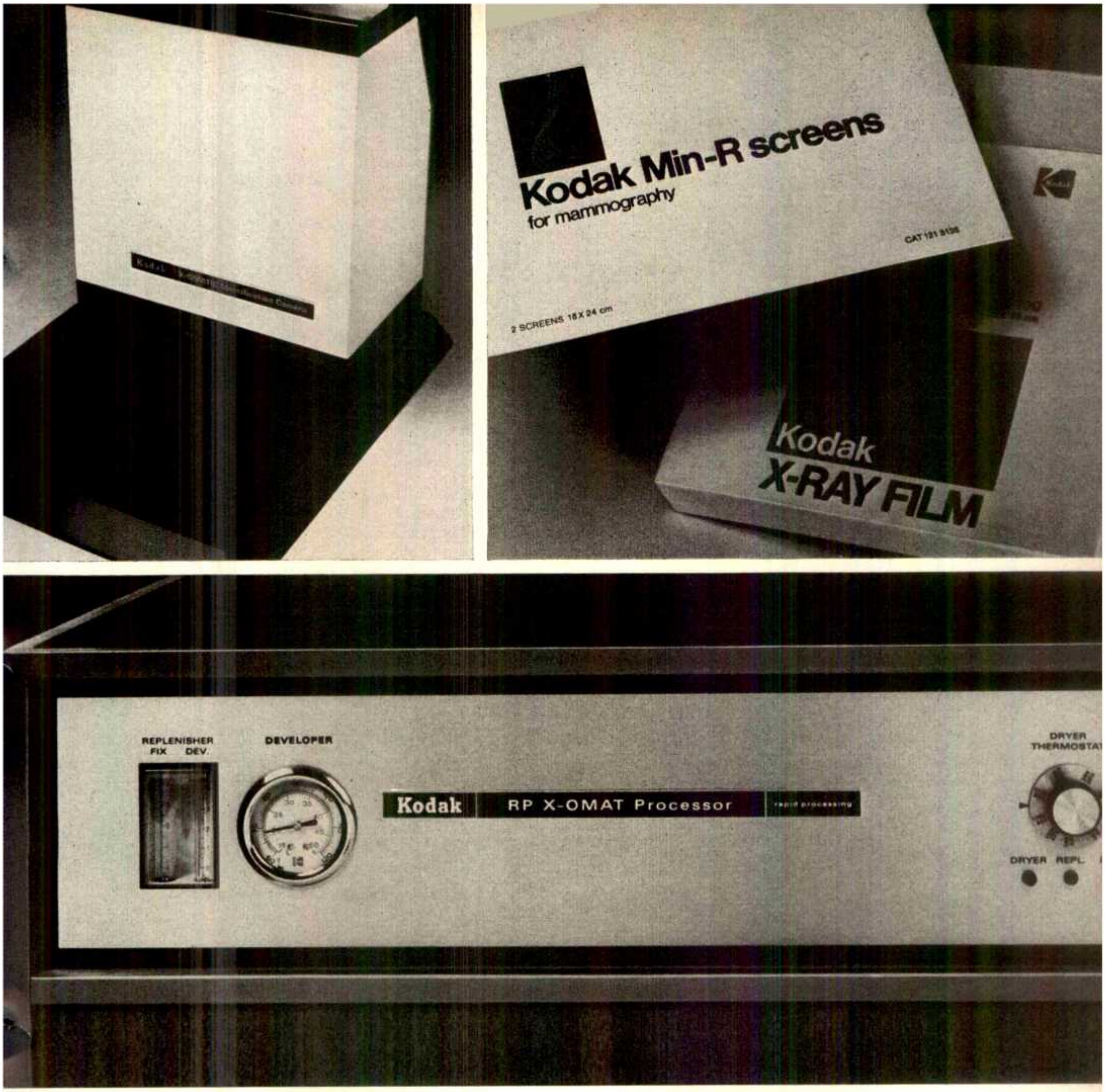

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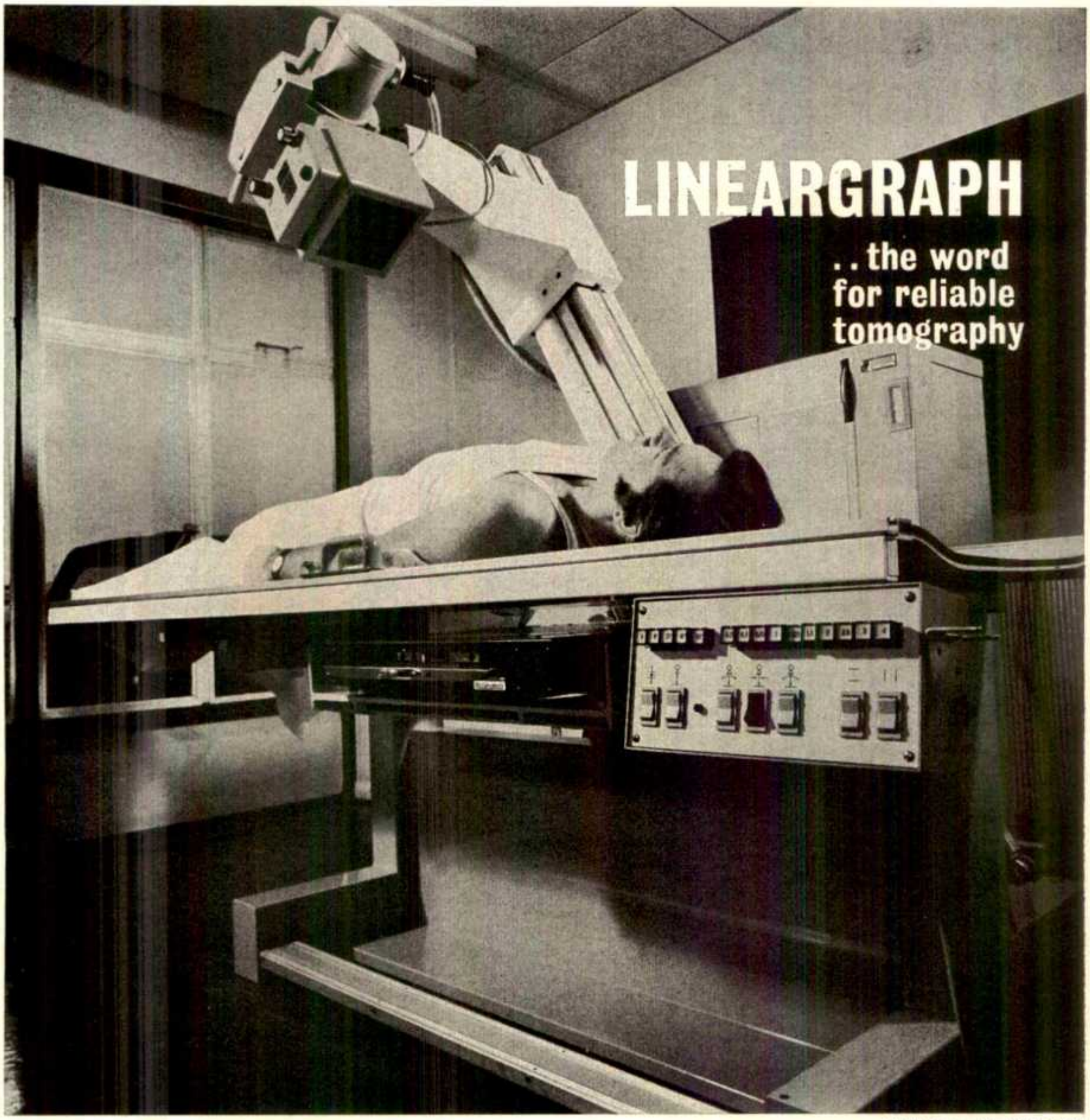

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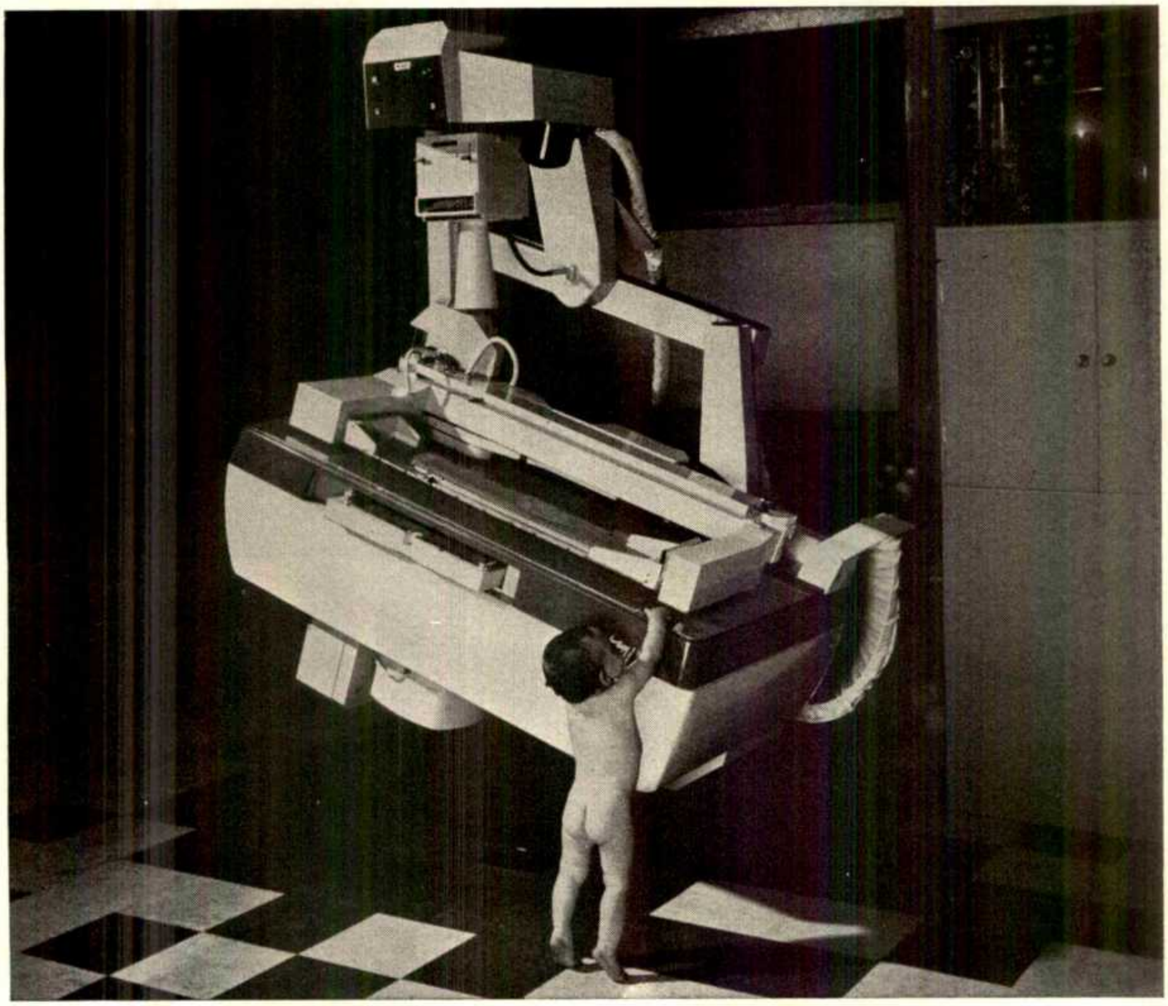

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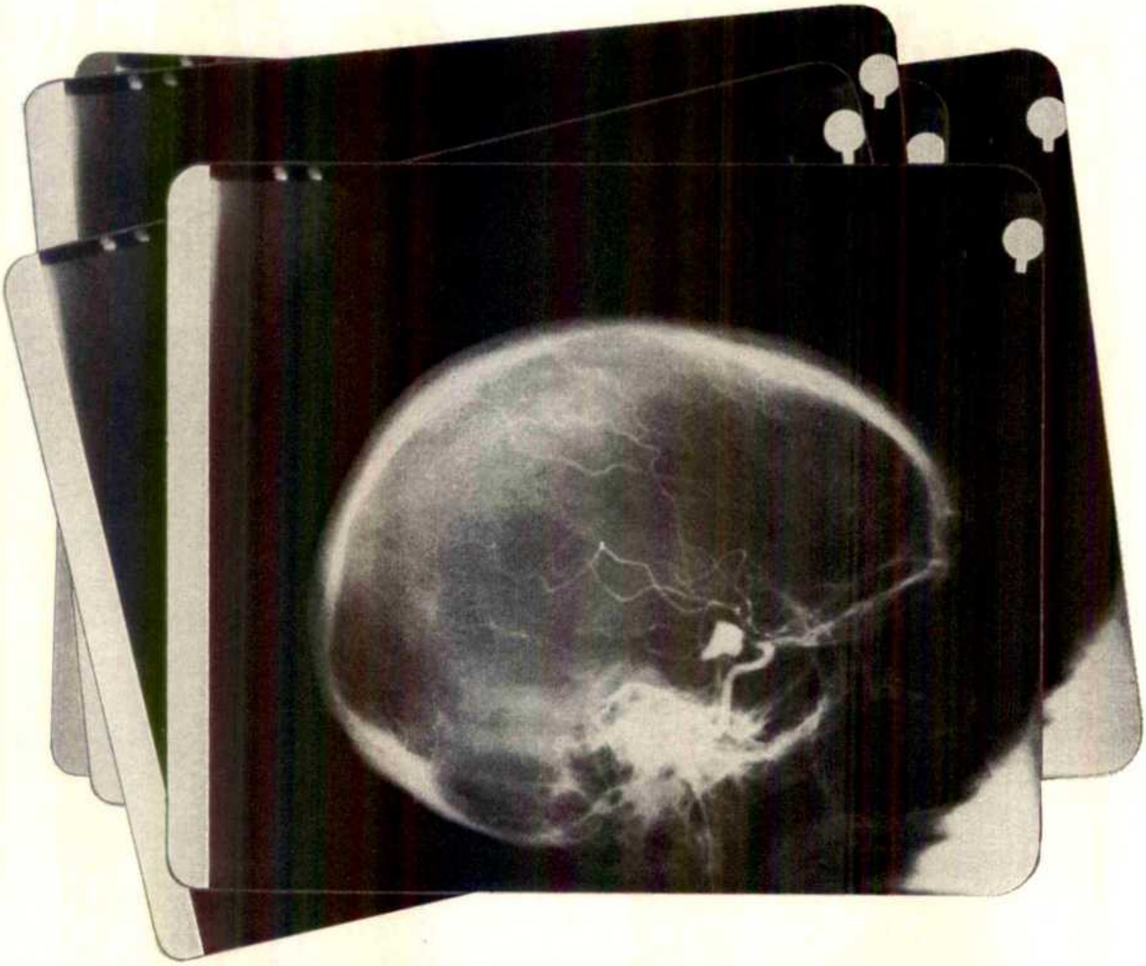

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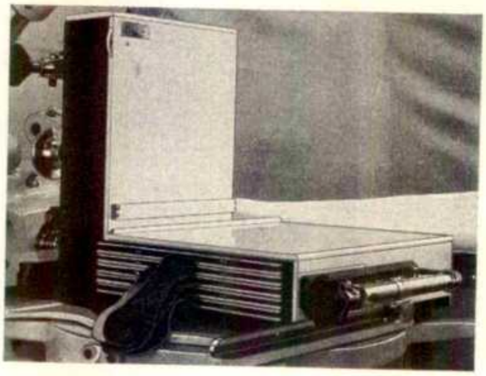

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1977, *British Journal of Radiology*, *50*, 299–301

VOLUME 50 NUMBER 593 MAY 1977

The British Journal of Radiology

Radiology now

The Radiologist's dilemma*

The growth in the demand for diagnostic radiology continues throughout the world. In Britain estimates vary, but a growth rate of between 5 and 10% per annum has been reported from many centres, and there is no evidence that a plateau has been reached.

It is theoretically possible to meet the demand by increasing resources, and an attempt has been made to do this. According to Raison (1976) the number of diagnostic radiologists increased by 15% between 1967 and 1972, but the workload in the same period rose by 30%, so that the demand exceeded capacity to meet it. At a time when many new and exciting developments are taking place in diagnostic radiology there is anxiety that the increasing workload could result in decreasing quality of radiological work.

It is, therefore, opportune to evaluate whether the increase in the use of radiology has been beneficial. Very little is known about how diagnostic radiological procedures influence the subsequent management of the patient. From time to time there is also a need to look at what has become established practice, in order to decide whether it still serves a useful purpose, or whether there should be change or even complete abandonment.

A careful history and full clinical examination appear to have been superseded by routine radiological studies and extensive laboratory investigations. In some special situations such as intensive care units the daily ward round is replaced by the daily chest radiograph. Physicians in the U.S.A. have been forced into such practices by medico-legal requirements. Patients demand to be investigated in the mistaken belief that if diseases are diagnosed early enough then all will be well. Unfortunately financial rewards can also play a part in this policy.

Every radiologist is acutely aware of the problems of over-usage within his own department, particularly by accident and emergency units. There is evidence that a good deal of such work is carried out for medico-legal purposes. Radiologists have known for a long time that radiography of the skull in cases of trauma is of little value. Particularly is this so if the examination is carried out on patients who are drunk or unconscious and unable to co-operate. However, irrespective of the severity of the injury, skull radiographs are considered mandatory in such patients if they attend hospitals.

Careful studies (Loop and Bell, 1971; Roberts and Shopfner, 1972) have shown that there is no significant correlation between fractures of the skull and symptoms, or between the type of fracture, symptoms and physical findings. From this it is clear that the extent of injury to the intracranial contents is of major importance, and that the presence or absence of a fracture seldom affects treatment. Roberts and Shopfner suggested that skull radiography should be reserved for patients in whom a depressed fracture is suspected, or in location of suspected foreign bodies. Sub-dural haematomata often occur in the absence of a demonstrable skull fracture. Unfortunately some doctors, many lawyers and all patients consider that to detect a skull fracture is of importance.

Jones and Roberts (1976) examined the reasons underlying casualty officers' referral for radiographic examination. They found that 44% of all requests were made purely for medico-legal purposes. Concordance between the casualty officer's opinion and the radiologist's report was in the region of 97%. The observed discordance in no way prejudiced the patient's subsequent treatment and management.

Pilling (1976) has pointed out that as the profession has made radiology a routine request rather than the consequence of a clinical decision, it has over the years created an accepted procedure. This situation is dearly loved by the legal profession because it is identifiable, and adherence to it is a matter of fact rather than opinion. He argued that the law will ask the right questions if the criteria for radiography are changed. It would then be impossible for an expert witness to say that the normal practice would have been to request radiology.

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*Reprints from: Prof. K. T. Evans, Department of Diagnostic Radiology, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN.

Mygind and Vestermark (1974) reviewed 158 children with epilepsy to assess the value of routine radiography of the cranium. In 149 cases the skull radiographs were normal and in nine cases abnormalities were encountered, but in no cases were there changes of diagnostic, therapeutic or prognostic significance. They concluded that routine radiography of the cranium is unnecessary in such children without focal changes and with otherwise normal histories. Some reduction in the workload could be safely achieved according to Bull and Zilkha (1968) if patients with symptoms such as headache and vertigo, but without physical signs, were investigated by a lateral skull radiograph only.

Excretion urography is a time consuming and costly examination, and yet the number of requests for this examination is steadily rising. Atkinson and Kellett (1974) commented on the large number of urograms in their patients with hypertension that were completely normal. Following careful analysis of their material they advised that excretion urography in patients with hypertension should be reserved for patients under 40 years of age, or in whom there was a previously recognized renal abnormality.

The routine use of chest radiography in apparently healthy people is now being questioned. It is the view of the Department of Health and Social Security that the low incidence of pulmonary tuberculosis found in survey work no longer justifies the general need for mass radiography. Despite considerable opposition the number of mass miniature units has now been reduced. Although the incidence of carcinoma of the bronchus continues to rise there is virtually no evidence that detection of this disease at an earlier stage affects the prognosis favourably.

It has become standard practice to request pre-operative chest radiographs before patients are given general anaesthetics, irrespective of their age or whether they have signs or symptoms of disease of the chest or cardio-vascular system. Kerr (1974) has suggested that the benefits should be weighed against the risks, and advised against routine pre-operative chest X-rays. He identified certain high risk groups such as patients with respiratory and cardio-vascular symptoms, smokers over the age of 50, and immigrants who have not been examined previously. Retrospective and prospective studies of the value of chest radiographs before operation have been reported by Rees *et al.* (1976). They showed in their series that no abnormalities of any kind were detected under the age of 20, and there were no significant abnormalities under the age of 30. Furthermore, if in the absence of symptoms, findings on previous chest radiographs had been accepted for pre-operative purposes, 38% of the subjects in this study would have been spared further irradiation.

There is general concern regarding the great increase in referrals for examinations such as barium studies, in radiological investigations of the elderly, and lumbar spine radiography in low back pain. A survey of the incidence of abdominal radiography in pregnancy by Carmichael and Berry (1976) revealed that in some major hospital centres up to 34.8% of all pregnancies were subjected to this examination. They suggested that the criteria for radiological examinations in pregnancy need closer scrutiny.

Radiologists themselves are not free from blame. Not so long ago clinicians were encouraged to refer patients for radiological examinations. The flood gates are now open and the radiologist is attempting to close them without much success. It is important that the clinical problem should be identified and that the radiological method chosen is the correct one. Hard data must be obtained on the value to the patient of certain aspects of radiology, so that shortcomings can be pointed out. Examples have been described where the yield no longer justifies the expenditure.

It may not be possible to change, at a stroke, the habits of a lifetime, but we must now make great efforts to educate medical students and house officers so that only clinically useful radiology is requested. The Royal College of Radiologists, with the support of the Department of Health and Social Security, is about to start on a series of multicentre trials in an attempt to assess the current usage of radiology, and thus to suggest guidelines for radiologists and clinicians. Full consultation with other Royal Colleges and Faculties will be necessary if our efforts are to be successful. Reduction in unnecessary work will give the radiologist time to practise better, more interesting and more productive radiology.

K. T. Evans

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ROBERTS, R. and SHOPFNER, C. E., 1972. Plain skull roentgenograms in children with head trauma. *American Journal Roentgenology, Radium Therapy and Nuclear Medicine, 114*, 230–239.

Book review

Complications in Diagnostic Radiology. Edited by G. Ansell, pp. 509, 1976 (Oxford/London/Edinburgh/Melbourne, Blackwell Scientific Publications), £18·00.

There is an angiocardiogram of a catheter-perforated ventricle on the wrapper of this formidable book. It is only one of many (beautifully printed) pictures to make the radiologist reader wince. At one level the volume might be taken as a collection of horror stories, painstaking, comprehensive and spine-chilling.

However, the book is much more than that. Dr. Ansell is one of 19 contributors, all experts in their fields, and he leads us through most of the things which can go wrong in radiology. There are 23 chapters. Six deal with angiography in various territories. All the other current contrast examinations have a chapter each. Some overlap in the discussion of contrast medium reactions is inevitable with this lay-out, but does not intrude on the reader's patience. There are chapters on anaesthetic, radiation, isotope and ultrasound problems. Electrical and mechanical hazards are not forgotten. The last chapter reprints Dr. Ansell's "Notes on Radiological Emergencies", already a firm favourite in wall chart form.

I think this book performs a valuable service in carefully assembling and documenting what we must learn to avoid. Not everyone may wish to read it at once from cover to cover like a reviewer, but many will want to dip into it to resolve particular problems. It is remarkably complete for this reference function. Has your patient just swallowed a cupful of plaster of Paris instead of barium from a mislabelled container? Stop panicking and look it up in Ansell, helped by a good index.

The volume's sensible approach is illustrated by the mention of Murphy's law. This, you remember, has to do with the natural cussedness of things, with toast always falling buttered side down. Dr. Ansell's version runs: "If the design of equipment, or the method of performing a procedure, provides scope for a serious error to be made then, sooner or later, someone will inevitably make that error. Conditions in an X-ray Department provide ample scope for the operation of Murphy's law . . . " We have to know about hazards in our daily work in order to be able to guard against them. This book helps to do just that, and must be welcomed, however painful its subject matter. I am changing my ways of doing certain procedures after reading it. It is to be recommended to departmental libraries everywhere.

THOMAS SHERWOOD.

1977, *British Journal of Radiology*, *50*, 302–311

Radiological aspects of the vertebral components of osteochondrodysplasias

By S. Schorr, M.D.

Professor of Radiology, Tel-Aviv University School of Medicine; Head, Diagnostic X-ray Departments, Municipal Government Medical Centre Tel-Aviv/Yaffo

and C. Legum, M.D.

Lecturer in Paediatrics, Tel-Aviv University School of Medicine; Head, Genetics Unit, Municipal Government Medical Centre, Tel-Aviv/Yaffo

(*Received January, 1976 and in revised form August, 1976*)

ABSTRACT

Analysis of the individual components of the vertebrae permits the radiologist to identify and understand the fundamental physio-pathologic growth mechanisms affecting shape, size and architecture which operated during development. The achievement of this goal is facilitated by systematically paying attention to changes of the vertebral end-plates, anterior and posterior aspects of the vertebral body, the vertebral rim, neurocentral junction and interpedicular distance. The dynamic changes noted in follow-up studies of the spine in certain dysplasias may reveal the developmental history of the vertebral complex. The dimension of time is an important factor, which the radiologist has a unique opportunity to exploit. Vertebral configuration permits radiological analysis and diagnosis.

The tendency when describing spinal dysplasias is to emphasize the growth disturbances of the cartilaginous end-plates of the vertebral body, while neglecting the other components of the vertebra. Each element (the vertebral body, both end-plates and the neural arch) has its own intrinsic growth properties. However, growth and development of the various components of the vertebrae are interdependent and cannot be dissociated. The individual vertebra is an anatomical structure with both static and dynamic functions. Much can be learned about the whole vertebral complex by studying the aberrant growth and development of the dysplastic vertebra. The radiologist can study only those developmental phases which can be visualized on the radiograph, *i.e.* the ossification but not the chondrogenetic phase. By using the important dimension of time, the radiologist can achieve some retrospective understanding. Any change in the vertebral complex from infancy to adult life is a dynamic continuum. The abnormal morphologic configuration and size of a single or a group of vertebrae is the result of reactive responses to many factors and forces. These may be grouped under several headings: intrinsic, constitutional, dysplastic factors; extrinsic forces, *i.e.* weight-bearing, muscle-tendon activity; metabolic and endocrine factors.

The fundamental mechanism of vertebral dysplasias is a disturbance in coordination of the various processes of bone growth and formation. Therefore, it is important to consider the overall changes produced by both enchondral and periosteal vertebral growth, rather than those of enchondral growth alone.

The purpose of this paper is to point out the growth behaviour of the components of the vertebral complex in some dysplastic conditions.

VERTICAL GROWTH (END-PLATES)

According to Schmorl (1928), the longitudinal growth of the vertebral body takes place by enchondral development through the epiphyseal end-plates. Bick and Coppel (1950) have shown that the body of the human vertebral grows like the diaphysis of a long bone with true proximal and distal epiphyseal plates. Furthermore, the body of the vertebra is subject to the same deforming factors which influence the growth of long bones. Therefore, the same pathologic conditions which affect the growing epiphyseal plates of long bones may affect the vertebrae. Growth of the vertebral body in the vertical plane or height takes place equally in the superior and inferior cartilaginous end-plates (Schmorl 1928; Knutsson 1961; Bick and Coppel, 1950), which play the dominant rôle in vertebral growth. A defect in the end-plates of the vertebral body has a greater impact in producing deformity than a defect in the periosteal growth potential.

In tubular bones a delay in enchondral growth with continuing periosteal growth results in the production of short thick bones with flaring ends. In vertebral dysplasias this dual combination produces an effect on vertical, sagittal and transverse growth resulting in flattened vertebral bodies.

Platyspondyly (flat vertebrae) is not a fully satisfactory term because it refers only to the vertical diameter and fails to emphasize the accompanying defects in other vertebral components and diameters.

An adequate description of morphological vertebral changes should include the antero-posterior (sagittal on the lateral view) and transverse diameters (on the A.P. view), defects of the neural arch and the interpedicular distance. Platyspondyly is

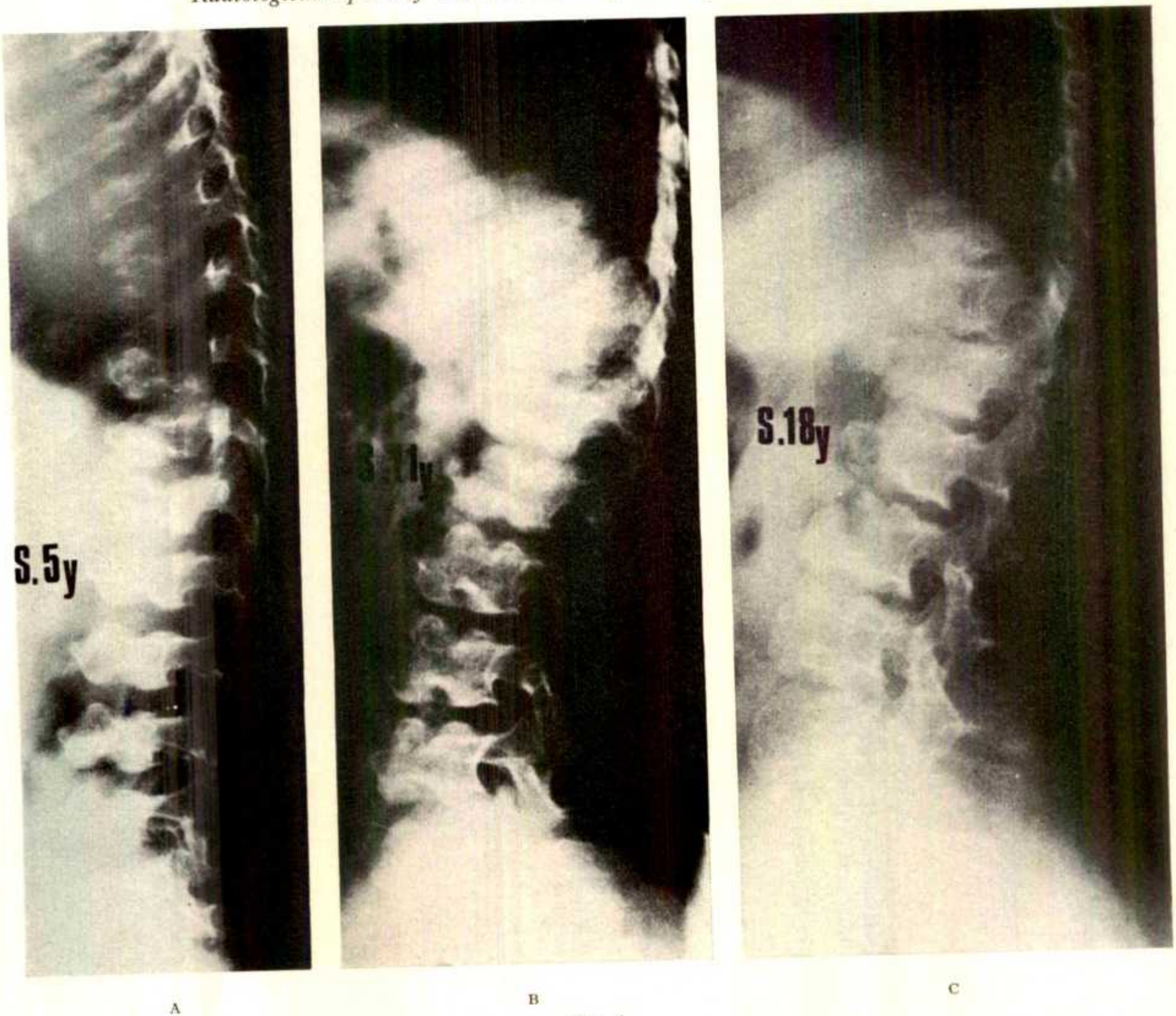


FIG. 1.

S., female, at 5, 11 and 18 years of age. Dyggve-Melchior-Clausen disease (DMC). Generalized platyspondyly, double hump-like elevation of both end-plates with central constriction, posterior scalloping and anterior cut-off.

usually the dominant, but not the sole feature in defective growth of the vertebrae. While the enchondral body growth lags behind, periosteal growth may increase the circumference of the vertebral body.

The superior and inferior end-plates are affected differently in various chondrodysplastic conditions. It seems that it has not been sufficiently stressed that the end-plate does not behave uniformly along its entire surface in various dysplasias. Thus, in Dyggve-Melchior-Clausen disease (DMC), the vertebral end-plates have a double elevation deformity and a central constriction with a double camel-hump like appearance (Figs. 1A, B, C) (Table I), a sign that together with a typical pelvis and iliac crest establishes the diagnosis (Schorr *et al.* 1977.)

TABLE I

RADIOLOGICAL FINDINGS IN DYGGVE-MELCHIOR-CLAUSEN (DMC) DISEASE: SPINE

Generalized platyspondyly
Double camel-humps with constriction
In the centre of both vertebral end-plates
Anterior vertebral cut-off or pointing
Posterior scalloping
Normal interpediculate distance
Hypoplastic odontoid process
No hypoplastic vertebrae
No gibbus
No horizontal os sacrum

In x-linked recessive spondyloepiphyseal dysplasia tarda (SED tarda), the end-plate has a single

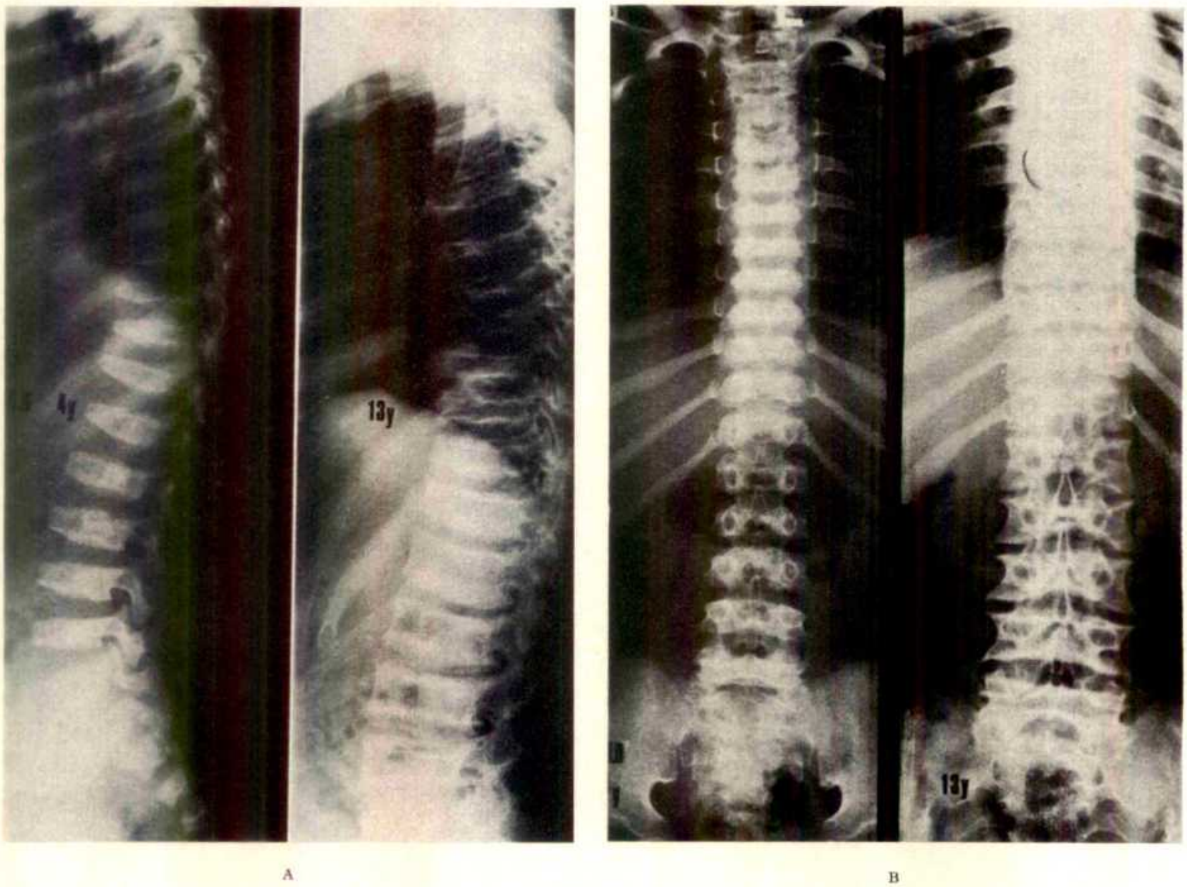


FIG. 2.

H.F., female, at four and 13 years of age. Spondylometaphyseal dysplasia (SMD). Generalized platyspondyly, increased sagittal and transverse diameters, lateral to the pedicles manifested in early childhood. The vertebral bodies, especialy in the thoracic region, are pointed anteriorly.

hump which slopes gradually from the centre posteriorly. Spranger (1975) considers this to be a valuable diagnostic sign.

In spondylometaphyseal dysplasia (SMD) the end-plate surfaces are irregular, with no elevations or humps (Figs. 2A, B) (Table II).

TABLE II

SPONDYLO-METAPHYSEAL DYSPLASIA (SMD): SPINE

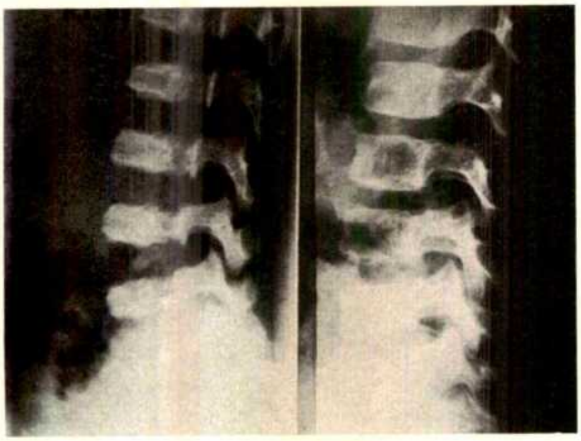
Generalized platyspondyly
Increased ant.-post. diameters of vertebral body
Extension of the transverse diameter
External to the pedicles
Anterior pointing especially of thoracic vertebrae
Irregular end-plates, no elevation
Lumbo-sacral IPD equal or normal

In spondyloenchondrodysplasia there exists a severe disturbance of chrondroosteogenesis, resulting in thickened flat, irregular end-plates (Schorr *et al.*, 1976) (Figs. 3A, B, C, D).

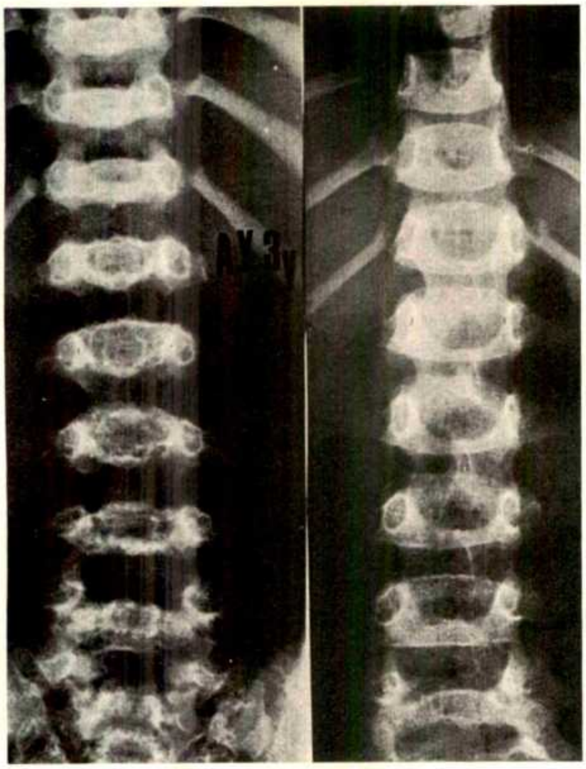
In Morquio's disease there is a central oval configuration of the end-plate during childhood which becomes flattened and rectangular in adulthood (Fig. 4). In the heterozygous form of achondroplasia, the vertebral body is small and cuboid in early childhood but has a regular flat end-plate in later childhood (Figs. 5A, B, C, D).

In thanatophoric dwarfism the severely flattened vertebra has a "H" or "U" shaped end-plate deformity on the antero-posterior view and marked central notching on the lateral view (Figs. 6A, B).

The epiphyseal or vertebral ring of Bick (Bick and Coppel, 1951) is primarily a cartilaginous structure which ossifies separately and behaves as an apophysis. This ring takes no part in the growth of the vertebral body. Small calcified foci appear in the cartilaginous rims at about seven to nine years of age. These calcified foci gradually ossify and fuse with the vertebral body to form the bony vertebral rim around the twelfth year. By 17 years of age, the spongiosa of the vertebral body has penetrated into the bony vertebral rim and can no longer be distinguished radiologically (Schmorl and Junghans, 1971). In certain dysplastic conditions there is a definite delay in fusion of the vertebral ring, which produces distortion of the anterior superior and inferior corner of the vertebral bodies. Thus, in achondroplasia and in the Hunter-Hurler mucopolysaccharidoses involvement of the vertebral ring produces some distortion of the anterior corners of the vertebral bodies which may have an irregular or rounded-off appearance (Figs. 7A, B). In Morquio's disease, the vertebral ring is irregular and grossly distorted and ossification and fusion to the vertebral body is severely delayed (Fig. 4).



A



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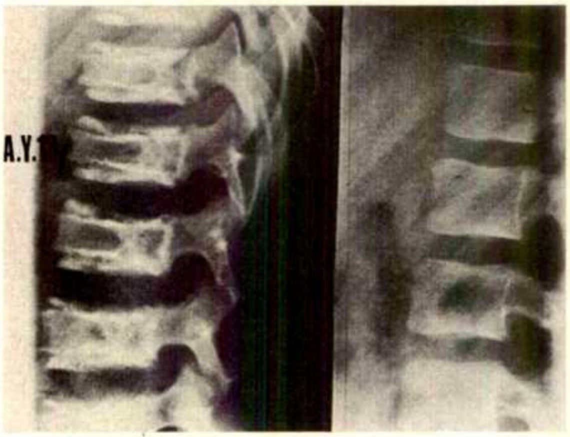

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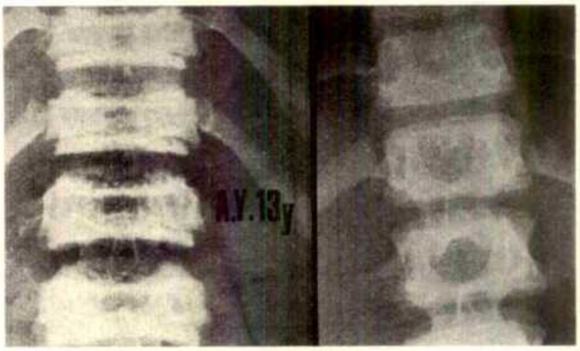

D

FIG. 3

A.Y., male, aged three years and 13 years. Spondyloenchondrodysplasia. A.P. and lateral views of spine (normal male radiograms of the same age on the right for comparison). Note the generalized platyspondyly, irregularity of both end-plates, islands of unossified cartilage and lack of ossification of the neurocentral junction in the vertebral bodies. At 13 years—note especially the increased A.P. and lateral diameters and the markedly disturbed chrondro-osteogenesis.

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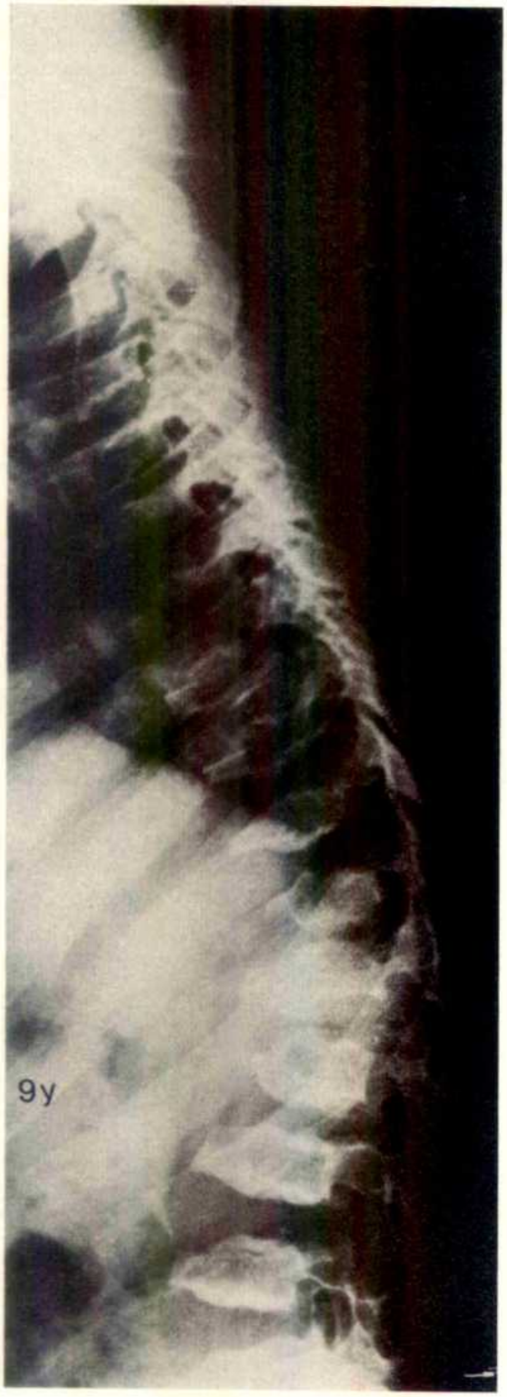


FIG. 4.

D.L., female, nine years of age. Morquio's disease. Note the flattened-oval shaped vertebrae with anterior tonguing, especially in the lower thoracic vertebrae. Hypoplastic first lumbar vertebral body. The vertebral rings are grossly distorted. Scalloping of the posterior aspects of the vertebral bodies.

HORIZONTAL AND SAGITTAL GROWTH OF THE VERTEBRAL BODY (CIRCUMFERENTIAL GROWTH)

Horizontal and sagittal growth takes place by periosteal membraneous bone formation. Knutsson's (1961) observations on the growth of the vertebral body in Scheuermann's disease indicate that the sagittal (antero-posterior) growth does not occur concentrically to the same extent in all directions from the centre of the vertebral body. Appositional growth takes place at the anterior surface of the vertebral body, but not on the posterior surface. Erdheim (1931) demonstrated that in acromegaly, periosteal ossification by apposition of new bone is greatest anteriorly, slightly less on the lateral surfaces and absent on the posterior surface.

In spondyloepiphyseal dysplasia tarda, the generalized platyspondyly is accompanied by an apparent increase in the anterior-posterior diameters and a short anterior aspect of the vertebral body resulting in a trapezoid-triangular shape. In addition there is anterior pointing of the vertebral body.

In spondylometaphyseal dysplasia (SMD) (Figs. 2A, B) there is an increase in the anterior-posterior diameter, mainly as a result of growth external to the pedicles.

In both Dyggve-Melchior-Clausen disease (DMC (Fig. 1) and spondyloenchondrodysplasia (SEnD) (Figs. 3A, B), the anterior-posterior diameter of the vertebral body is greater than that found in normal controls of the same age and sex. In adults, there is a tendency for the increased antero-posterior diameter to diminish and approximate to the normal.

Swischuk (1970) has postulated that the thoraco-lumbar hooked or notched anterior aspect of the vertebral body frequently seen in infants and young children is due to muscular atonia and the exaggerated normal physiologic kyphosis of this age. This results in anterior herniation of the nucleus pulposus with intravertebral disc narrowing. Although this sequence of events is plausible, there are additional intrinsic growth disturbances at the anterior and lateral surfaces. Morphologic abnormalities at the anterior and lateral vertebral borders are not limited to the thoraco-lumbar region but also occur in the upper and mid-thoracic and lower lumbar regions. These changes are well demonstrated in the genetic mucopolysaccharidoses as in Hunter's disease (Figs. 7A, B) and in Dyggve–Melchior–Clausen disease (DMC) (Figs. 1A, B, C).

THE NEURAL ARCH AND POSTERIOR ASPECT OF THE VERTEBRAL BODY

According to Schmorl (1928), the ossification processes involving vertebral bodies and vertebral

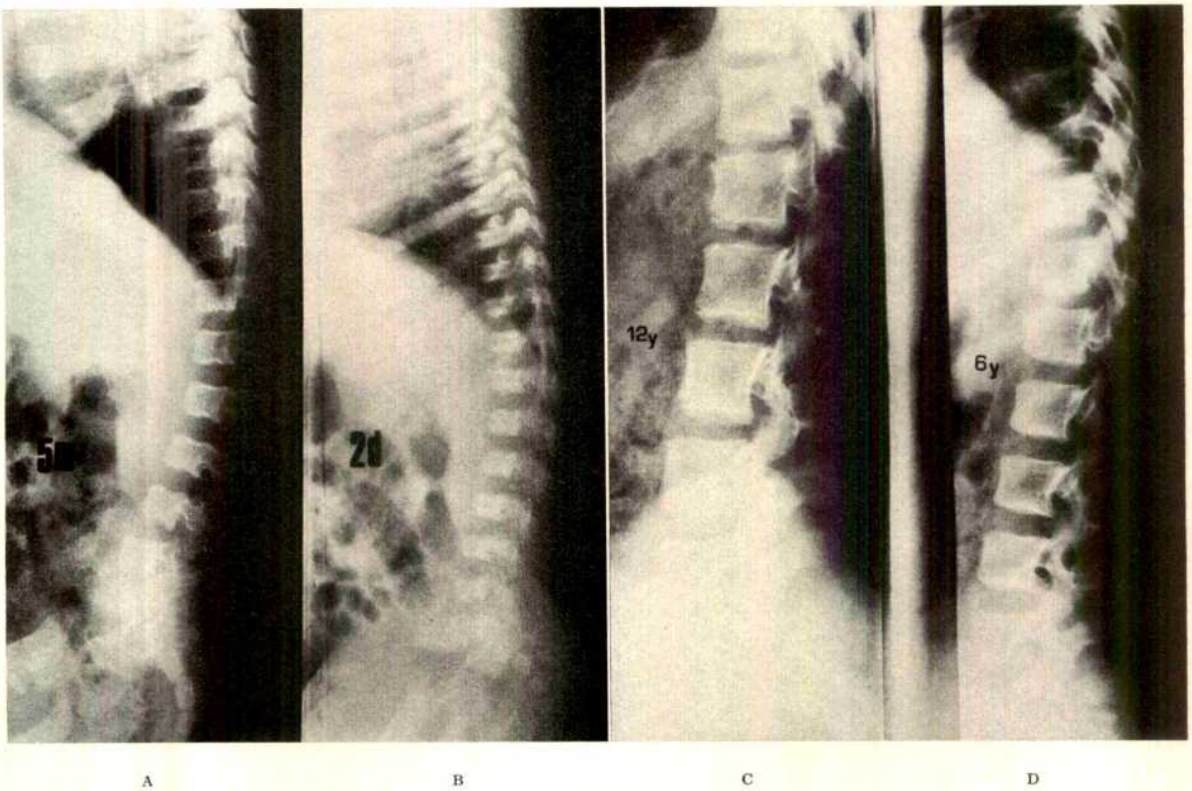


FIG. 5.

B., female—(A) at 2 days of age, (B) 5 months of age, (C) 6 years of age, (D) 12 years of age. Achondroplasia. The vertebral bodies are cuboid in infancy and rectangular in childhood. Short pedicles, narrow canal, scalloping of the posterior aspects of the vertebral bodies, increasing with age.

arches are not uniform. Enchondral ossification of the vertebral body develops with the ingrowth of blood vessels, while the vertebral arch develops by perichondral ossification. Since growth takes place only anteriorly and laterally and not posteriorly, the posterior margin of the vertebral body is established at birth. The bony spinal canal is limited anteriorly by the vertebral body. The growth of the vertebral arch determines the development of the spinal canal. The main site of growth of the arch is the cartilage bridging the arch and the vetebral body (*i.e.* neurocentral synchondroses). As the arch grows backward due to continuous growth at the cartilaginous bridge, the distance between the pedicles and the sagittal (A.P.) diameter of the spinal canal increases. The sagittal diameter of the spinal canal increases fairly rapidly from birth until five to ten years of age. The bridge between the vertebral body and the arch gradually fuses between the third and the sixth year of life. Thereafter, the neural arch grows by deposition and resorption of bone.

Shortening of the pedicles due to delayed dysplastic enchondral growth at the neuro-central junctions (NCJ) will reduce the antero-posterior diameter of the spinal canal. There is also a shortening of the lumbo-sacral interpedicular distance and exaggeration of the concavity of the posterior vertebral body surfaces ("scalloping") (Mitchell, 1967). Marked posterior concavity of the vertebral body is commonly seen in dysplastic conditions such as in achondroplasia (Figs. 5A, B, C, D) and hypochondroplasia, in certain mucopolysaccharidoses and mucolipidoses, such as Hunter's disease (Figs. 7A, B), Morquio's disease (Fig. 4) and in Dyggve–Melchior–Clausen disease (DMC) (Figs. 1A, B, C).

Variations in the interpedicular distance seem to be able to occur independently of vertebral body development. The lumbosacral interpedicular distance (IPD) seems to be an almost independent component of vertebral development. Thus, there are some dysplastic conditions in which the main

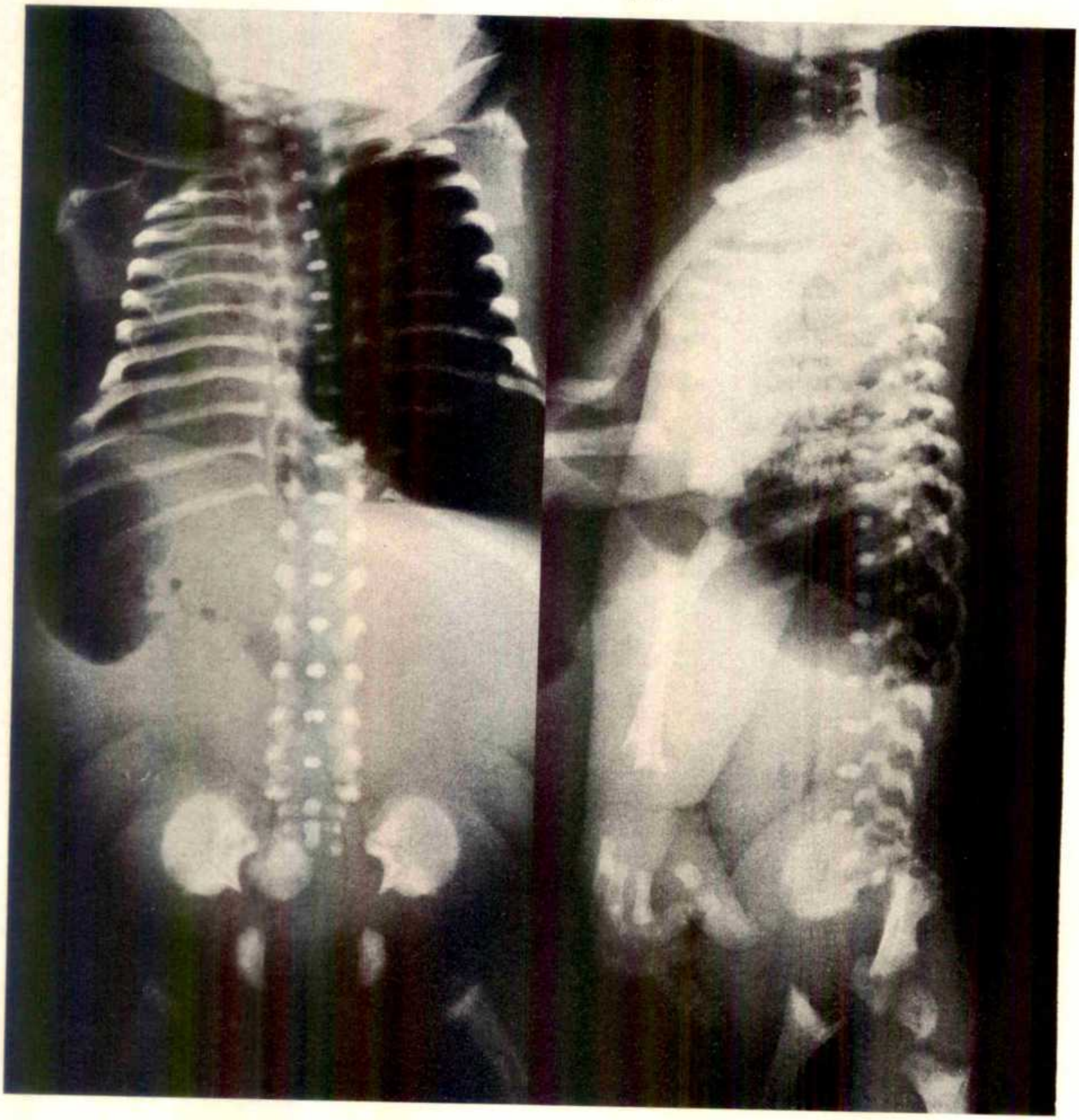
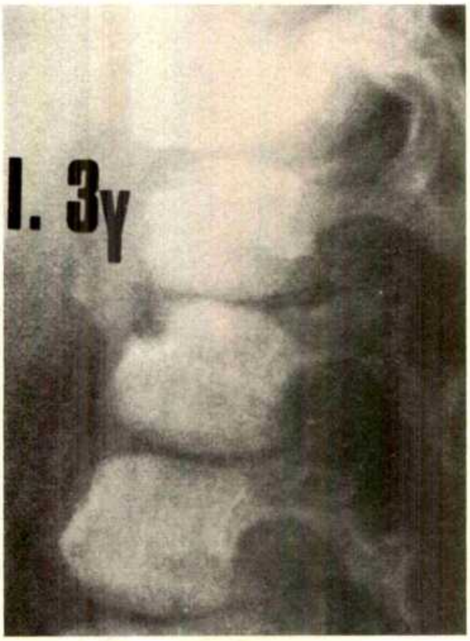


FIG. 6.

A stillborn female with thanatophoric dwarfism. Severe generalized platyspondyly, wide disc spaces. (Gas in the aorta and vessels.)

feature is a constant narrowing of the lumbosacral IPD, achondroplasia (Fig. 8) and hypochondroplasia (Fig. 9).

Even though scalloping is a main feature of certain dysplasias, as illustrated in Hurler-Hunter, Morquio and DMC disease, the interpedicular distance is not reduced in these conditions. Only in achondroplasia and hypochondroplasia do IPD and scalloping co-exist. In diastrophic and metatropic dwarfism, the lower lumbo-sacral IPD may show



A

Fig. 7.

Hunter type of mucopolysaccharidosis.

(A) J., male, three years old. Note the involvement of the antero-superior vertebral corner, mild scalloping.

(B) Z.I., male, eight years old. Note the marked scalloping and hypoplastic and fifth lumbar vertebrae.

the normal progressive increment or may remain constant.

The delay in maturation of the neuro-central junction (NCJ) is well illustrated in spondylo-enchondrodysplasia (SEnD) (Figs. 3A, B). In this condition, the NCJ does not fuse until late adolescence.

It is most important to stress the time factor in the appearance of radiological signs in dysplastic conditions of the vertebra. While certain conditions are already present at birth (Table III) or even recognizable occasionally in intra-uterine life, some dysplastic states are detectable during infancy and early childhood (Table IV), whilst others are only recognizable later in childhood (Table V).

TABLE III

Dysplastic vertebra manifested at birth

Thanatophoric dysplasia (ThD)
Achondrogenesis
Achondroplasia (hetero-, homozygous)
Chondrodysplasia punctata
Metatropic dwarfism
Spondylo-epiphyseal dysplasia congenita (SED cong.)
Osteogenesis imperfecta congenita (OIC)

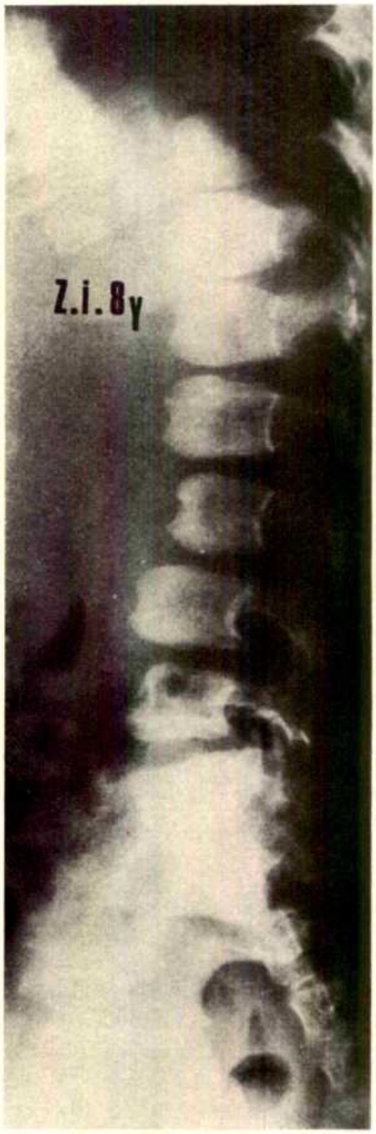


Fig. 7B.

TABLE IV

Dysplastic vertebrae manifested in early childhood

Hurler-Hunter (MPS I, II)
Morquio (MPS IV)
Dyggve-Melchior-Clausen (DMC) disease
Spondylometaphyseal dysplasia (SMD) (Kozlowski)

TABLE V

Dysplastic vertebrae manifested in late childhood

Multiple epiphyseal dysplasia (Fairbank)
Spondyloepiphyseal dysplasia tarda (SED tarda)
Pseudoachondroplastic dysplasia
Mucolipidoses
Osteogenesis imperfecta tarda

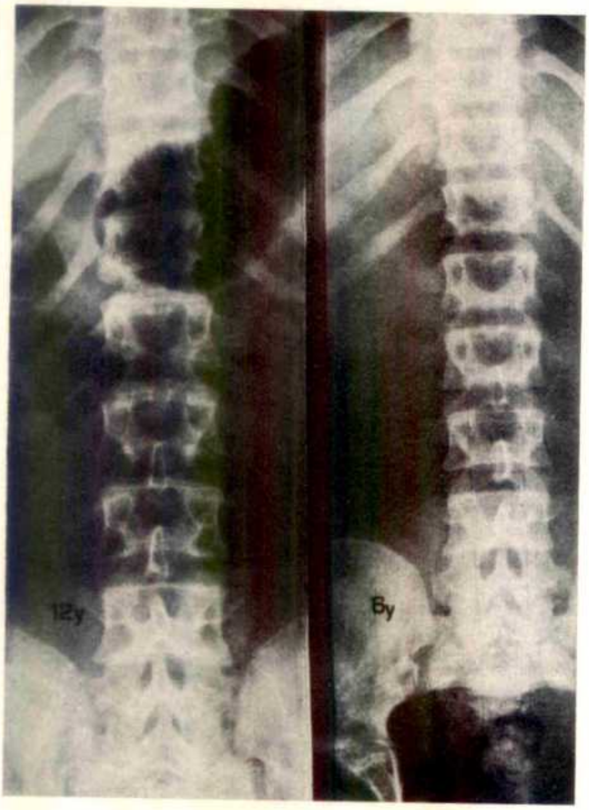


FIG. 8.
S.R., female, at six and 12 years of age with achondroplasia. Note the characteristic progressive narrowing of the interpediculate distance in the lumbo-sacral region.

SUMMARY

The normal growth of a vertebral body is analogous to the normal growth of a tubular bone. In dysplastic conditions the vertebra is subject to similar abnormal growth factors. Various aspects of the separate vertebral components in dysplastic growth are discussed. The radiological features of dysplastic conditions of vertical growth (end-plates), the apophyseal rings, sagittal and horizontal (circumferential) growth, the posterior vertebral body aspect, the neuro-central junction and the lumbo-sacral interpedicular distance are analysed separately. The differential radiological features of the dysplastic spine in various clinical entities are described. The importance of the time factor in differentiating between these entities is documented.

Dysplastic changes should lead to further investigation of growth in the normal and diseased states.

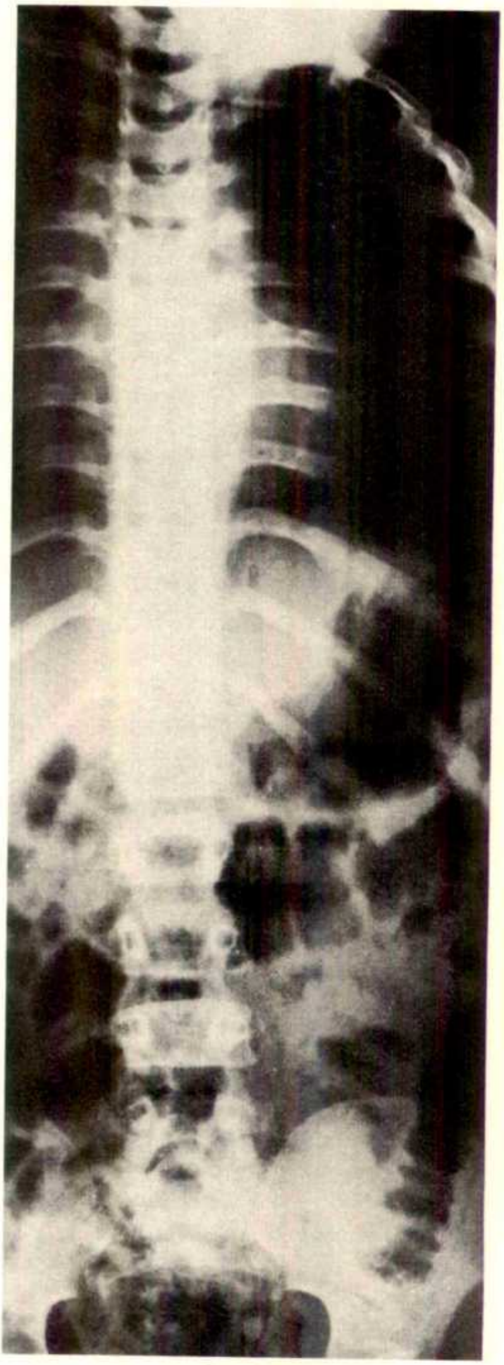


FIG. 9.
B.R., male, five years old with hypochondroplasia. Narrowing of the lumbo-sacral interpediculate distance.

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Book review

Bones and Joints (Monographs in Pathology—No. 17). Edited by L. V. Ackerman, H. J. Spjut, and M. R. Abell, pp. xi+349, 190 illus., 1976 (Baltimore, The Williams and Wilkins Company), £27·00.

The long course on diseases of bones and joints, sponsored in 1975 by the United States – Canadian Division of the International Academy of Pathology, was aimed at "continuing education for pathologists and clinicians", and this publication will undoubtedly accomplish this objective.

The 17 contributions are introduced via embryology and bone structure, followed by two chapters on radiology, two on immunology and 11 on clinical pathology and morbid anatomy, these embracing metabolic bone disease, osteomyelitis, idiopathic aseptic necrosis, arthritis, Paget's disease and a wide range of tumours. With several exceptions the style is mainly discursive and all may be read with profit; some are outstanding, notably the sections devoted to infections, aseptic necrosis, arthritis, synovial tumours and giant cell lesions.

The two chapters by radiologists are devised to help pathologists and clinicians, and the more senior radiodiagnostician will gain but little here in his own speciality, although perusal of the chapters commended above certainly aids the correlation of radiological changes with the underlying pathology.

An extensive bibliography and ample subject index are provided, and the illustrations are mostly well selected and reproduced. Few mistakes mar this book, but one deplores the substitution of a radiograph print of a radius and ulna for a humerus claimed to be the first recorded chrondroblastoma of the diaphysis of that bone. One confusing legend was noted, and the last chapter has the quaint running title of "small tumors of bone". Whilst not seriously detracting, these and other textual errors give the impression that the prestigious editors (or their underlings) have sometimes been "caught napping" in performing an otherwise praiseworthy exercise.

C. H. G. PRICE.

1977, *British Journal of Radiology*, *50*, 312–313

"Pulseless" femoral arteriography

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ABSTRACT

Direct needle arteriography of "pulseless" femoral arteries is described. The information obtained, and the excellent detail of the arterial tree, is discussed in cases of collateral filling of the femoral artery. Evaluation of occluded by-pass grafts is also mentioned.

In cases of obstruction of one iliac artery where the collateral circulation fills the femoral artery on the affected side, direct needle puncture femoral arteriography is usually not performed because the femoral artery pulse is absent. Injection of contrast material through a needle inserted into the opposite femoral artery or through a catheter in the distal abdominal aorta will show considerable dilution of contrast and therefore, considerable decrease in opacification of the circulation in the affected lower extremity. Considerable improvement in visualization and therefore, adequate preoperative evaluation could be achieved by direct puncture of the "pulseless" femoral artery. Furthermore, patients who have had a by-pass graft inserted in the past and who show decrease in circulation with absence of femoral pulse, are also good subjects for such a procedure.

TECHNIQUE

Following the introduction of an 18G or 16G arterial needle into the femoral artery from the unaffected side, power injection of 50 ml of contrast is given over two seconds with multiple exposures of the distal abdominal aorta and iliac-femoral artery area. Usually, patients that show absence of a femoral pulse on one side, will demonstrate narrowing or obstruction of the common iliac or external iliac artery with collateral circulation and reconstitution of the femoral arteries on that side. If the "pulseless" femoral artery is opacified on the later film, it is punctured with an 18G arterial needle. The films exposed in serial sequence will show the position of the femoral artery and visual comparison with the needle inserted on the unaffected side is helpful. Hand injection of 30 ml of water soluble dye is then given and films of the pulseless extremities are taken. The only contraindications may be a recent episode of embolism because of the dangers of dislodgement of the embolus by such a procedure.

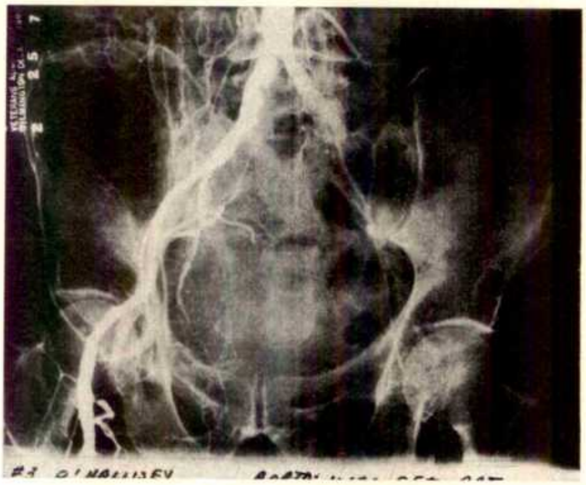

FIG. 1.

Aortoiliac study—plaque formation in the left common iliac artery with complete obstruction. Large plaque in the right common iliac artery and decrease in caliber of the right external iliac artery.

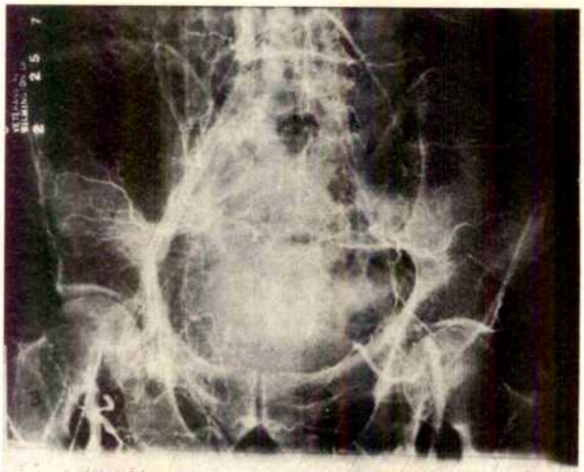

FIG. 2.

Aortoiliac study—late arterial phase. Reconstitution of the left common femoral artery.

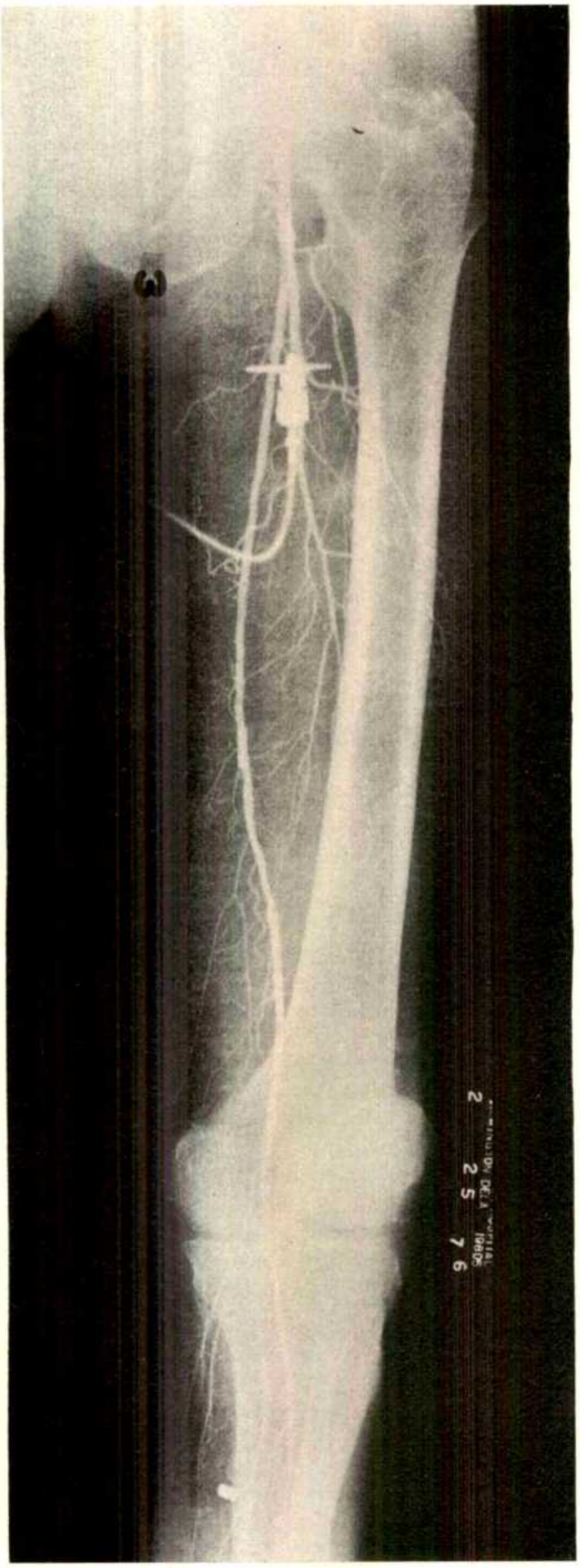

Fig. 3.

Femoral arteriograms—occlusion right superficial femoral artery with collateral reconstitution. On the left, no obstruction seen except in the distal popliteal area.

In the past four years we have performed direct needle puncture of pulseless femoral arteries as a routine. No similar method has been described in the literature (Schobinger and Ruzicka, 1964).

Case Report

The following case is presented for illustration.

A 69-year-old, cachectic, white male with +1 femoral pulse on the right side and absent pulse on the left side. He had arteriosclerotic heart disease and was on nitroglycerine for chest pain.

Aortoiliac study showed extensive arteriosclerotic disease with narrowing of the lumen and formation of plaques in the right iliac system and in the major vessels in the right leg. There was complete obstruction of the left common iliac artery proximal to the origin of the external iliac and hypogastric arteries (Fig. 1). The left common femoral artery filled through collaterals (Fig. 2). Good opacification of the femoro-popliteal system on the left was obtained following direct puncture of the pulseless left femoral artery (Fig. 3).

The patient was placed on anticoagulants with slight improvement. Further treatment was deferred. No follow-up.

Discussion

Our series of cases comprises 30 patients with unilateral absence of the femoral pulse. We were successful in performing arteriography on that side in 27 cases (90%). There was no major complication that could be demonstrated. Even when haematomas occur they appear to be smaller as the circulation is apparently much slower then on the unaffected side. There was no evidence of complete occlusion with gangrene or pregangrenous changes in any of the patients following this procedure. In three patients percutaneous puncture of the pulseless femoral arteries could not be performed and after two or three attempts, no further efforts were made. On the other hand, cases in our series demonstrated excellent flow in the femoral-popliteal-trifurcation area even though obstruction in the iliac artery systems was noted and the femoral pulse was absent.

The information obtained by this method is much greater than by injecting the abdominal aorta or the affected iliac artery.

Acknowledgment

The author wishes to thank Mr. R. Little and Mr. R. Herman, Medical Illustration Service for the high quality photographs and Mrs. M. Gibson and Miss D. Cushing for typing of the manuscript.

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Effect of cobalt-60 gamma rays and DTIC (5-(3,3 dimethyl-1-triazeno)-imidazole-4-carboxamide) on human malignant melanomas grown in athymic nude mice

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(*Received October, 1976*)

ABSTRACT

The effects of ^{60}Co γ rays and DTIC on two human malignant melanomas, inoculated and passed serially in athymic mutant nude mice, were studied *in vivo*. Dose-response curves determined after single exposures to ^{60}Co γ radiation indicate that human malignant melanomas remain radioresistant after transplantation in mutant nude mice. A fractionated irradiation régime, used in the treatment of patients suffering from malignant melanomas, had a considerable effect but did not cure. A corresponding treatment régime with DTIC inhibited the tumour growth, but less effectively than ^{60}Co γ rays. These two treatments combined were more effective than either alone. The results obtained show no disagreement with results from clinical practice regarding treatment of disseminated malignant melanomas. This suggests that human malignant tissue, transplanted to mutant nude mice, retains its properties with respect to response to therapy. The mutant nude mouse may therefore be valuable in developing new treatment régimes for cancer.

The thymus-deficient mutant nude mouse (Isaacson and Cattanach, 1962; Flanagan, 1966; Rygaard, 1973) accepts transplanted heterologous tissue, *e.g.* human tumours, because of defects in the T-cell compartment of the immune apparatus. Histological and cytological appearances, *i.e.* structural and ultrastructural features, of human malignant tissue grown in the mutant nude mouse are in full accordance with those of the original tissue (Povlsen and Rygaard, 1971; Povlsen and Rygaard, 1972). Chromosome analyses have shown that neither total chromosomal species shift nor hybridization take place in this heterotransplantation system (Visfeldt *et al.*, 1972). The human enzyme pattern and the human species specific antigens of Burkitt's lymphoma are shown to be maintained when this tumour is transplanted to the mutant nude mouse (Povlsen *et al.*, 1973). The mutant nude mouse may therefore be of great value in therapeutic cancer research, but it still remains to be seen whether human malignant tissue inoculated into this laboratory animal and malignant tissue in man have common properties with respect to response to therapy.

The purpose of this work is to shed light on the response of human malignant melanomas, grown in the mutant nude mouse, to ^{60}Co-radiation and DTIC.

MATERIALS AND METHODS

Animals

Young nu/nu/BALB/C/BOM mice were used for the experiments. The animals were kept in a special room at 27°C with automatically regulated 12-hour dark and light periods, under conventional but very strict conditions.

Tumour material

E.K. malignant melanoma was taken from a lymph node metastasis on the left side of the neck of a 20-year-old man. Examinations with a light microscope showed that the tissue was composed of large polygonal cells with light basophilic cytoplasm and large vesicular round-oval nuclei with distinct and eosinophilic nucleoli. Some of the cells stained positive for melanin and typical melanosomes were seen with the electron microscope. Numerous mitoses were found as well as areas with necrosis and inflammation.

E.E. malignant melanoma was taken from a lymph node metastasis in the left axilla of a 62-year-old man. The histological features of this tumour were similar to the former.

Inoculation and measurement of tumour size

The tumour tissue was cut into representative cubes approximately $2 \times 2 \times 2$ mm in size and inoculated subcutaneously on the dorsal surface of the animals immediately after surgery. After 1–3 weeks the grafts started to grow, and the mice developed non-invasive tumours histologically indistinguishable from the original tumour. The tumours had grown in the mutant nude mouse for several passages when the experiments described here were performed.

Two axes of the tumour were measured with calibrated calipers and the cross-section of the tumour, calculated as being an ellipse, was used as a parameter for the tumour size.

Dosimetry and irradiation procedure

The animals were irradiated locally without anaesthesia at a source-skin distance of 80 cm, by

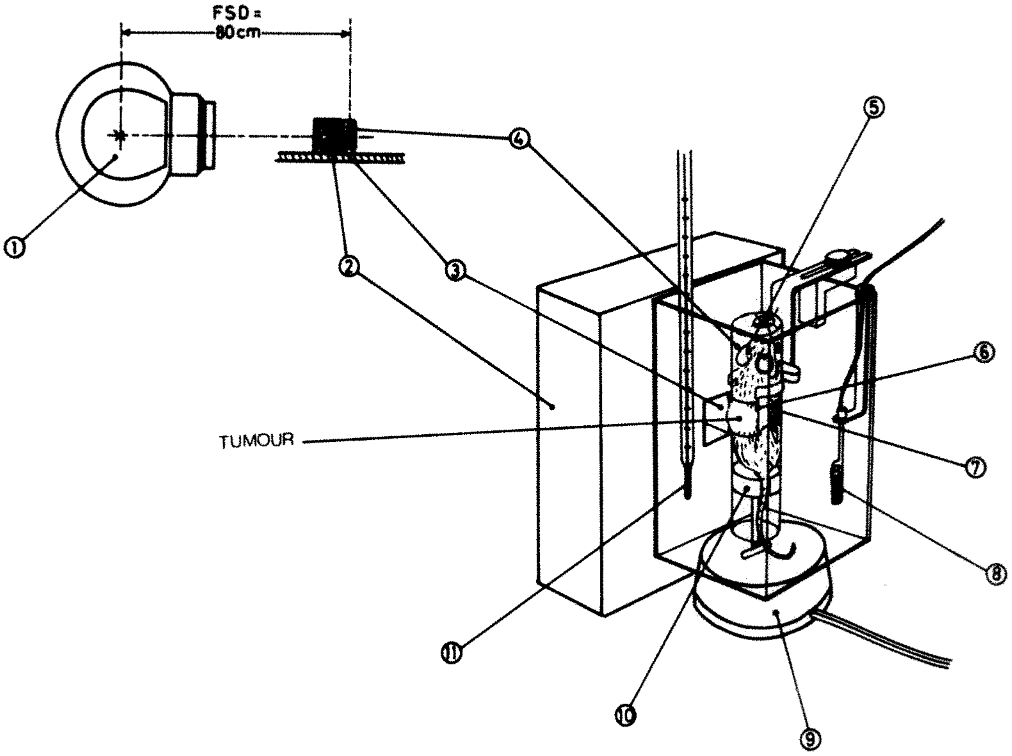

FIG. 1.

Experimental arrangement for irradiation of tumour transplants in nude mice. The mouse was placed in a Perspex holder (4) and partly immersed in water. A hole (5) in the "cranial" end of the mouse holder allowed the mouse to breathe freely. A piston arrangement with a slit to fit the tail (10) prevented the mouse from moving. A wad of cotton wool (7) just opposite the tumour made the tumour protrude out of an opening (6) cut in the holder. A thermostat regulated heating element (8) kept the temperature of the water (11) at any predetermined value. A magnetic stirrer (9) agitated the water. A ^{60}Co Mobaltron therapy unit (1) aligned horizontally was used to irradiate the tumour tangentially at an FSD = 80 cm through a 14 × 14 mm brass-lined aperture (3) in an 8 cm thick lead block (2).

applying one tangential field from a 5000 Ci ^{60}Co therapy unit (TEM, Mobaltron 80). The experimental arrangement for irradiation is illustrated in Fig. 1. The mice were placed in thin-walled Perspex tubes (4) with a large hole (5) in the "cranial" end through which they could breathe freely. A piston arrangement in the "tail" end (10) positioned the animals firmly in the tube. A wad of cotton wool (7) made the tumour protrude through an opening (6) cut in the mouse-holders.

Acceptable dosimetry conditions were obtained by partly immersing the mouse-holders in a water phantom whereby the entire tumour was positioned under water and at a distance from the outer surface of the phantom wall greater than that corresponding to the ionization maximum of the radiation used. The water temperature was kept at 30°C by a thermostat (8). The tumours were positioned for irradiation by means of the beam defining light of the therapy unit (1). A 14 × 14 mm brass-lined hole (3) through an 8 cm thick lead block (2) served as the beam defining aperture.

The depth-dose distribution and the isodose curves for the field at the appropriate SSD were determined from ionization chamber measurements in a tissue-equivalent Perspex phantom. Measurements made with thermoluminescent discs (TLD 100 LiF ribbon, Harshaw) placed at the ionization maximum varied within a few percent of the corresponding ionization chamber readings of 110.5 rad/min. The variation of dose within each malignant melanoma, based on isodose curves, was determined to be less than 5%

Further information concerning the experimental procedure was given in a previous article (Brustad *et al.*, 1976).

DTIC administration

DTIC was obtained from the National Cancer Institute, Bethesda, Md. It was dissolved in physiological saline and administered intraperitoneally in daily doses of 25 mg/kg body weight.

Histological examinations

At the conclusion of the experiments the tumours were dissected free, fixed in 4% buffered formaldehyde, embedded into paraffin wax, cut in 10μm sections and stained with hematoxylin and eosin.

EXPERIMENTAL TREATMENTS

Four different treatment régimes were tested.

1. *Single irradiation*

The available animals were divided into five groups. One group remained unirradiated and the other four groups received 400, 700, 1400 and 2100 rad, respectively.

2. *Fractionated irradiation*

The effect of an irradiation régime used in clinical treatment of malignant melanoma was studied. Groups of animals were exposed to 480 rad daily for five plus three days, with a two-day interval between the irradiation series.

3. *Chemotherapy*

Chemotherapeutic experiments were carried out with DTIC, an anti-cancer agent used in the treatment of malignant melanomas in the clinic. DTIC was administered in daily doses of 25 mg/kg body weight according to the same time pattern as described above for the fractionated irradiation. Clinical results show that DTIC exhibits very little dose and schedule dependency (Carter and Friedman, 1972; Klepp, 1975a).

4. *Fractionated irradiation combined with chemotherapy*

The fractionated treatment régime with DTIC described in paragraph 3 and the irradiation régime described in paragraph 2 were also combined. In

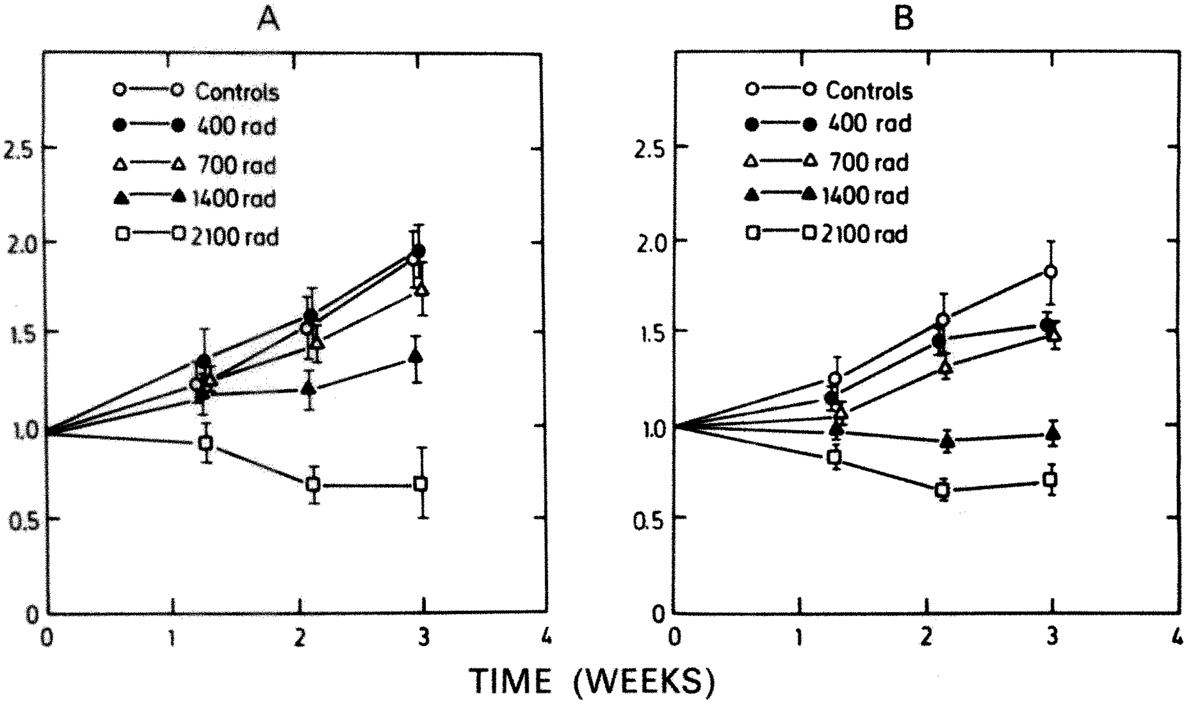

FIG. 2.

Alteration in tumour size as a function of the time elapsed after single irradiations as described under Experiments, section 1. The tumour sizes are normalized to unity at the day of irradiation. The vertical bars indicate the standard deviation of the mean. (A) refers to E.E. malignant melanoma. From top to bottom of the symbol list the data represent the mean of 7, 6, 6, 5, and 6 tumours.

(B) refers to E.K. malignant melanoma. From top to bottom of the symbol list the data represent the mean of 6, 4, 5, 5, and 6 tumours.

these experiments DTIC was injected one to two hours before the animals were irradiated.

All experiments were performed with both melanomas. For each treated group, one untreated group served as control. The observation period of the animals was limited to the time an adequate number of mice appeared healthy. The tumour sizes varied between 10 and 30 mm^2 at the start of the experiments.

Results

Dose response curves

The change in tumour size as a function of the time elapsed after single exposures to ^{60}Co radiation is shown in Fig. 2. There is only a slight difference between the growth of the tumours in the control group and that in the groups exposed to doses of 400 and 700 rad. The effect of higher doses is considerable. The ratio of the mean tumour size in the treated groups to that in the control group is plotted versus dose in Fig. 3.

Comparison of DTIC and ^{60}CO radiation

The tumour regression following fractionated exposure to ^{60}Co radiation only, fractionated treatment with DTIC only, and combined therapy involving both treatments is shown in Fig. 4. There is a considerable difference between the effect of DTIC and that of ^{60}Co radiation in favour of the latter. It also looks as if radio- and chemotherapy in combination have a greater effect than radiotherapy alone.

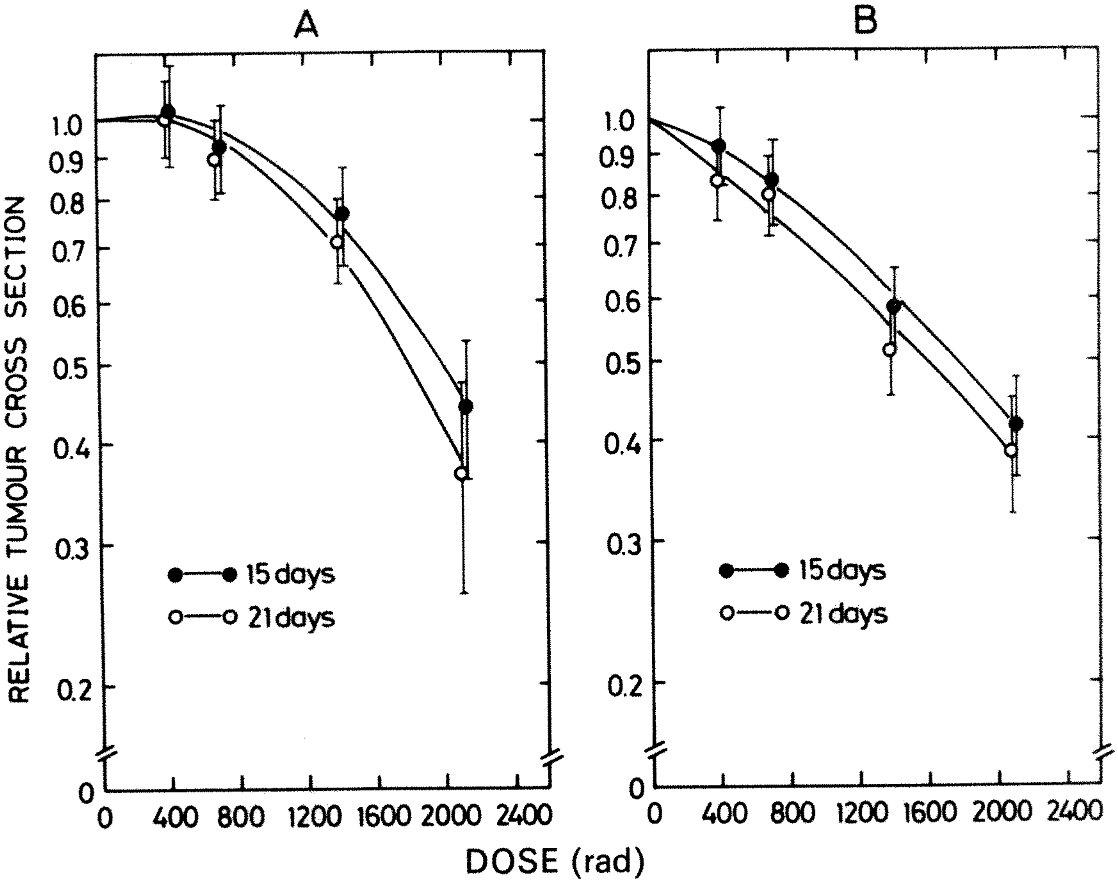

Fig. 3.

Dose-response curves for malignant melanomas. The ratio of the mean tumour size in the treated groups to that of the control group 15 and 21 days after single irradiations, as described under Experiments, section 1, is plotted versus dose. Polynomials of the second degree are fitted to the data by the method of least square. The scale is semilogarithmic.

(A) E.E. malignant melanoma.

(B) E.K. malignant melanoma.

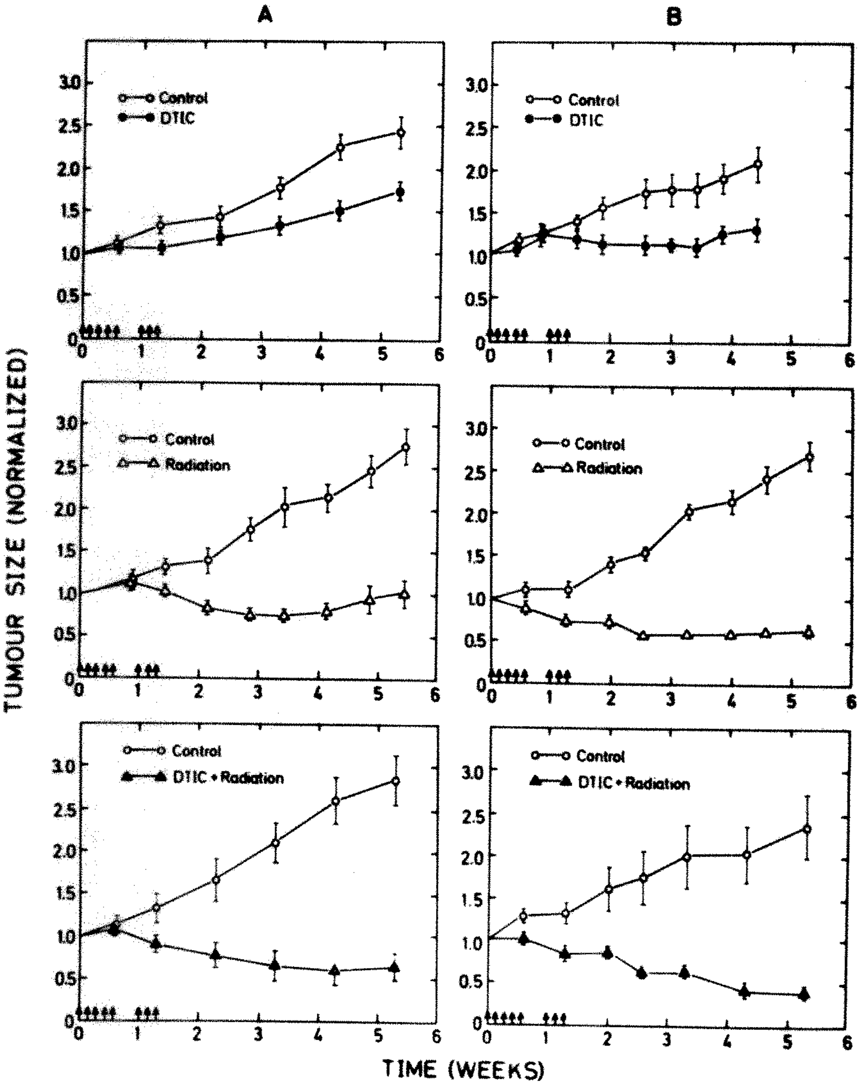

Fig. 4.

Mean tumour size as a function of time elapsed after the start of fractionated treatment. The tumour sizes are normalized at the start of treatment. The vertical bars indicate the standard deviation of the mean. The arrows symbolize the times at which the treatments were performed.

(A) E.E. malignant melanoma.

(B) E.K. malignant melanoma.

The upper figure shows results of chemotherapeutic treatment with DTIC, performed as described under Experiments, section 3. (A) Seven control animals and seven treated animals. (B) Four control animals and six treated animals.
The Middle figure shows results of fractionated irradiation performed as described under Experiments, section 2. (A) seven control animals and nine treated animals. (B) Five control animals and five treated animals.
The lower figure shows results of fractionated irradiation combined with chemotherapy, performed as described under Experiments, section 4. (A) Seven control animals and five treated animals. (B) Six control animals and five treated animals.

Histological examinations of E.E. malignant melanoma revealed that tissue from untreated animals and animals treated with DTIC showed almost the same histological picture. Centrally, necroses were found surrounded by a peripheral brim of polygonal vital cells, often in mitosis. Tumour tissue from animals having received radiotherapy and animals having received combination therapy also had a similar histological pattern which differed from the tissues described above. The necrotic areas were larger and looked like a network stretching throughout the tumour, but areas with surviving cells and several mitotic figures were also seen.

A similar investigation of E.K. malignant melanoma showed that the melanomas from mice treated with DTIC had large central and smaller peripheral necroses, some of which were calcified. The tissues differed from those of the control animals which showed central necroses only. Tumour tissue from irradiated mice was necrotic all over the tumour apart from small nests where vital cells and a few mitoses were observed. Combination therapy resulted in totally necrotic tumours with no obvious vital tumour cells left.

The measurements of tumour size and especially the histological examinations suggest that E.K. malignant melanoma might be more sensitive to treatment than E.E. malignant melanoma. This will be examined more closely in experiments performed on a larger scale with greater initial tumours.

Discussion

It is well known that advanced cases of malignant melanoma, where surgery is no longer applicable, are very difficult to cure. Both radiotherapy (Cade, 1948; Paterson, 1948; Rock Carling *et al.*, 1955) and chemotherapy (Luce, 1972) have commonly proved disappointing. However, recent clinical trials with DTIC alone (Luce *et al.*, 1970; Cater and Friedman, 1972; Ahmann *et al.*, 1972; Gerner and Moore, 1973; Einhorn *et al.*, 1973; Moon *et al.*, 1975) and in combination with other anticancer agents (Luce, 1972; Gerner and Moore, 1973; Einhorn *et al.*, 1974; Ahmann *et al.*, 1974; Gerner *et al.*, 1975) seem to show that malignant melanomas have a certain degree of response to chemotherapy. In the past few years clinical studies have indicated, in contrast to the previous ones mentioned above, that radiotherapy may in fact also be of considerable value in the treatment of inoperable malignant melanomas (Pearson, 1974; Sealy *et al.*, 1974). Few clinical data are available on combined radio- and chemotherapy of malignant melanomas, but it has been suggested that relatively high daily doses of radiotherapy combined with chemotherapy might give better results than the comparable fractionated régimes commonly used (Klepp, 1975b). In spite of some therapeutic progress made in recent years, the prognosis for patients suffering from disseminated malignant melanoma is still very poor.

Dose-response curves determined in the single-irradiation experiments with ^{60}Co radiation show that human malignant melanomas remain radioresistant after being transplanted to the mutant nude mouse. This is consistent with what would be expected from clinical practice, but contradictory to results obtained from single irradiation of animal (Dewey, 1971) and human (Barranco *et al.*, 1971; Thomson *et al.*, 1975) malignant melanoma cells grown in culture.

The data obtained from the clinically relevant experiments with DTIC and ^{60}Co radiation on human malignant melanomas grown in the mutant nude mouse are also in accordance with what would be expected from clinical experience with this disease. The same conclusion has been drawn by Povlsen in his experiments with CCNU, 5-FU and DTIC on a human malignant melanoma inoculated into the mutant nude mouse (Povlsen and Krag Jacobsen, 1975).

Although the two melanomas were grown in the same immunological surroundings, one of them is probably more sensitive to treatment than the other. This observation indicates that a different response to treatment of a given type of malignant disease is not necessarily due to a different immune response of patients, but may well reflect a difference in the cancer cells themselves *in vivo*.

The present findings suggest that the heterotransplantation system, human malignant tumour—mutant nude mouse, mirrors the clinical situation well. Of course, to explore the validity of this statement more closely it will be necessary to perform experiments where the results can be compared directly with tumour regression in the patient from whom the transplanted tumour was taken. Such studies will be undertaken. So far the mutant nude mouse seems to be a valuable tool in improving treatment régimes used in cancer therapy.

Acknowledgments

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The effect of radiation on tumour growth delay, cell survival and cure of the animal using a single tumour system

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ABSTRACT

The response of a murine tumour to single doses of X rays has been measured using three different assays—animal cure, cell survival *in vitro* after irradiation *in vivo*, and tumour growth delay. The dose to cure 50% of the animals, the TCD_{50}, was 79.0 Gy. This was not affected by clamping the tumours to render all the cells hypoxic at the time of irradiation, implying that most of the cells in the tumour were hypoxic already. The enhancement ratio for the hypoxic cell sensitizer Ro-07-0582 was 2.1. The cell survival assay gave an enhancement ratio of 1.6 and an hypoxic fraction of 5%. The discrepancy in the estimates of the hypoxic fraction can be explained by the ability of the naturally hypoxic cells, but not the oxic ones, to recover from potentially lethal damage *in vivo*. Neither the cell survival assay nor the growth delay assay agreed with the TCD_{50} assay as to the effect of the hypoxic cell sensitizer, even allowing for recovery from potentially lethal damage. It is doubtful whether the measured survival curve would predict the measured TCD_{50}.

The dose of radiation required to cure an animal of its tumour in the absence of an immune response is determined primarily by the sensitivity of the individual tumour cells to the radiation. The techniques at present available for directly measuring this sensitivity involve excision of tumours immediately after irradiation and assaying cell survival either *in vitro* (Barendsen and Broerse, 1969), or by injecting the cells into recipient mice (Hewitt and Wilson, 1959; Powers and Tolmach, 1963). If the survival curve parameters measured by such assays were those pertaining to the survival of the clonogenic cells when left in the tumour, one would expect that any agent which modifies the radiation response should do so equally for cell survival assayed directly, animal cure measured in terms of the TCD_{50} (the dose of radiation to cure 50% of a population of animals of their tumours) and tumour growth delay. This assumes that alterations in tumour growth after irradiation are primarily a reflection of the lethal effects of the radiation on the tumour cells (Thomlinson and Craddock, 1967; McNally, 1974).

Previous studies on a rat fibrosarcoma have shown that the modifying effects of oxygen and radiation quality on tumour growth delay and on cell survival *in vitro* after irradiation *in vivo* were not the same (McNally, 1973, 1975). It was suggested that assays which involve removal of cells from their normal environment after irradiation may not accurately reflect the course of events in the undisturbed tumour.

In order to study further the relationship between tumour cell survival *in situ* and *in vitro* and the effects of modifying agents on the survival, we have used a transplantable tumour designated "MT", chosen because it is possible to measure the effects of radiation on the tumour using all three end-points, cure of the animal, tumour regrowth and cell survival *in vitro* after irradiation *in vivo*. We have compared the effects of two modifying procedures on the radiation response of this tumour. These procedures are: clamping the tumour to render all the cells hypoxic and injection of the hypoxic cell sensitizer Ro-07-0582 (Roche Products Ltd) before irradiation to sensitize the naturally hypoxic cells in the tumour.

MATERIALS AND METHODS

The anaplastic "MT" tumour arose spontaneously in a WHT/Ht mouse in 1964, in Dr. H. B. Hewitt's animal colony, and has been maintained since then in the same inbred strain of mice. Its volume doubling time at the size used was about one day.

To obtain experimental tumours, a tumour of 5–10 mm in diameter was excised aseptically from a mouse, cut into fragments of less than 1 mm^3 and implanted subcutaneously by a fine trochar over the sacral region of the backs of eight-week-old female mice. Tumours reaching a mean diameter of 5.0–6.0 mm between seven and 21 days after implantation were selected for treatment. In some of the cell survival assays tumours up to 8 mm in diameter and some of those which arose as doubles were used. Irradiation was by X rays from a Pantak X-ray set operated at 250 kV and 15 mA (H.V.L. 1.3 mm Cu.) with an additional filter of 0.25 mm Cu. and 1 mm Al. The dose rate at the tumours was 4.3 Gy min^{-1} (1 gray equals 100 rad). The sacral region of the back of a mouse was irradiated, without anaesthetic, as previously described (Sheldon and Hill, 1977). Tumours could be rendered hypoxic by applying a clamp ten minutes before the start of irradiation. The clamps used were similar to those described by

Denekamp and Harris (1975). The hypoxic cell sensitizer Ro-07-0582 [1-(2-hydroxy-3-methoxypropyl)-nitroimidazole] was used at a concentration of 1 mg per g body weight. It was administered by intraperitoneal injection 30 minutes before the start of irradiation.

For cell survival studies, tumours were excised at various times after irradiation and single cell suspensions prepared as previously described (McNally, 1972). An aliquot of the cell suspension from an unirradiated tumour was then exposed in aerobic conditions to a dose of 80 Gy of ^{60}Co γ rays and 5×10^4 of these "feeder" cells in 3 ml of Eagle's Minimum Essential Medium plus 15% fetal calf serum and antibiotics were pipetted into each of a number of 50 mm plastic tissue-culture Petri dishes. Appropriate numbers of test cells were then added to the Petri dishes. Four replicate plates were used for each tumour cell suspension. The cells were incubated for 11 to 13 days at 37°C in a humidified atmosphere of 5% CO_2 in air. Macroscopic colonies were then stained and counted and survival curves were constructed. The plating efficiency was 30 to 50%.

Results

The curves relating the probability of local tumour control to the radiation dose and the dose required to control 50% of the tumours (the TCD_{50}) ± one standard error of the mean, were derived using a computer programme based on the logit method for maximum likelihood. Animals in which there were no recurrences 80 days after irradiation were scored as cured (Sheldon and Hill, 1977). The calculated curves are shown in Fig. 1 for the three conditions of irradiation used. The TCD_{50} in the absence of a clamp was 79.0 Gy (range of standard error of the mean 78.2 to 79.9 Gy). Applying a clamp ten minutes before irradiation had little effect on the TCD_{50} (Fig. 1), implying that most of the tumour cells were normally hypoxic (the calculated TCD_{50} was 77.8 Gy, but this was not significantly different from that for irradiation in the absence of the clamp). If the animals were given 1 mg/g Ro-07-0582, 30 minutes before the start of irradiation, the TCD_{50} was reduced to 38.0 Gy, giving an "enhancement ratio"* of 2.1 (Fig. 1).

Figure 2 shows the times for tumours to grow from a geometric mean diameter of 5.0–6.0 mm (irradiation size) to 10 mm after exposure to various doses of X rays, in the presence or absence of 1 mg/g Ro-07-0582. Each point represents data from at least 12 animals. The error bars represent ± 1 standard error of the mean. The drug clearly sensitized the tumours to radiation. Table I shows the enhancement ratio as a function of the dose of radiation, measured from the smooth lines drawn through the

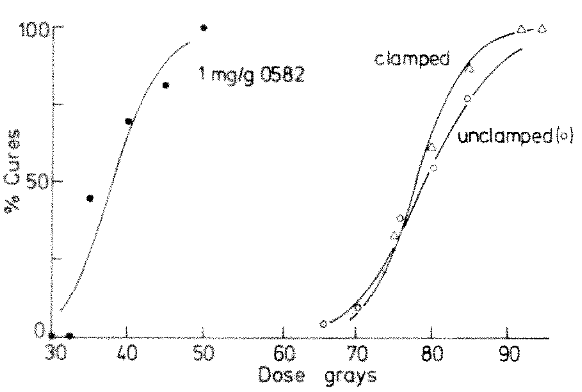

Fig. 1.

Tumour control probability versus X ray dose. Tumours were irradiated either unclamped (○), clamped (△) or unclamped 30 minutes after an intraperitoneal injection of 1 mg/g Ro-07-0582 (●).

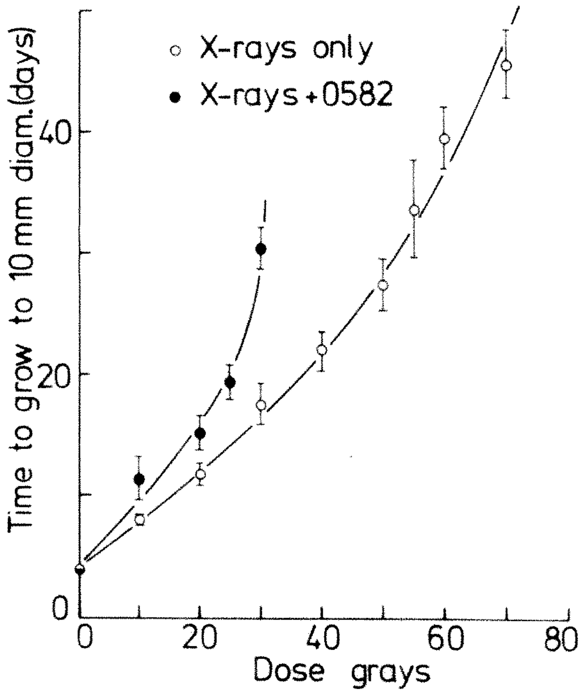

Fig. 2.

The time for tumours to grow from treatment size (5.0–6.0 mm) to 10 mm diameter versus the X-ray dose. Tumours were irradiated in the absence of (○) or the presence of 1 mg/g Ro-07-0582 (●). The error bars represent standard errors of the mean.

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* Enhancement ratio = X ray dose without the drug divided by X ray dose with the drug to cure half the mice.

TABLE I

Enhancement ratios for Ro-07-0582 (1 mg/g given 30 minutes before irradiation) for various final tumour diameters chosen for the regrowth assay

X-ray dose in absence of drug (Gy)	Drug enhancement ratio final diameter 9 mm	10 mm	12 mm
10	1.25	1.56	1.25
20	1.22	1.47	1.30
30	1.34	1.49	1.36
40	1.49	1.52	1.47
50	1.72	1.69	1.69

experimental points (as in Fig. 2) for three different final diameters, 9, 10 and 12 mm. Above a dose of about 40 Gy there was little difference in the measured enhancement ratios, but below this the enhancement ratio depended on the final size chosen.

Figure 3 shows survival curves for tumour cells from tumours irradiated *in vivo* and then immediately excised and assayed *in vitro*. Tumours were irradiated either clamped or unclamped in animals breathing air, or ten minutes after killing the animals by neck luxation. The clamping procedure was equally effective as killing the animals in rendering the tumour cells hypoxic (Fig. 3). The line through the survival values for hypoxic cells was fitted by eye,

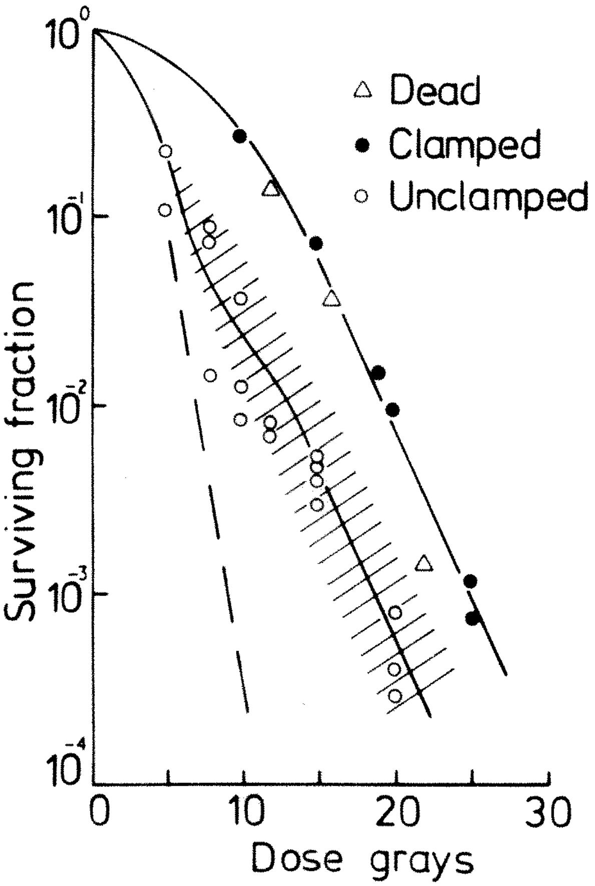

Fig. 3.

Survival curves for the cells of tumours irradiated *in vivo* and then immediately excised and plated *in vitro*. Tumours were irradiated in dead animals (△), or in live animals clamped (●), or unclamped (○). The line through the points for irradiation of clamped tumours was fitted by eye. The dashed line is a theoretical line obtained from this line by assuming an oxygen enhancement ratio of 2.7. The line through the data points for unclamped tumours was drawn assuming an hypoxic fraction of 5% and the hatched region represents the range from 2 to 15% hypoxic cells.

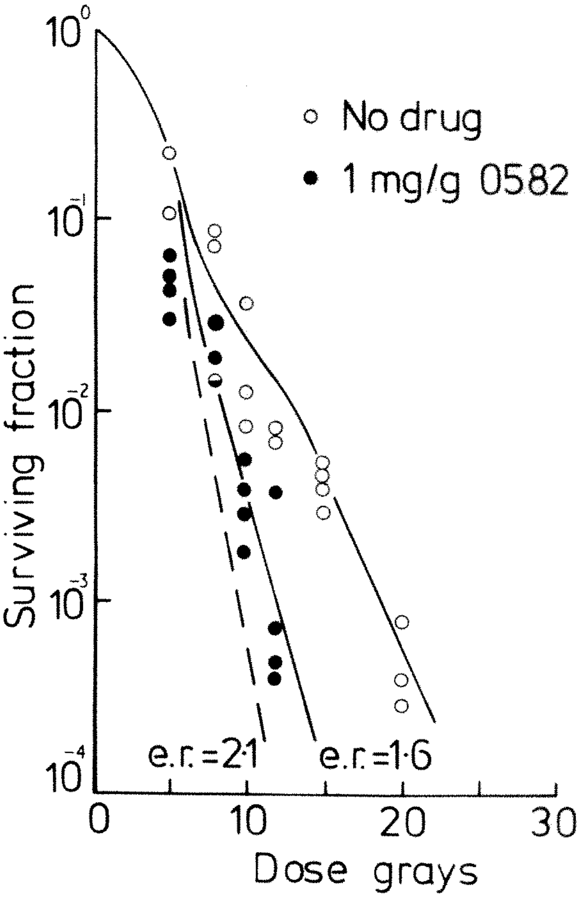

Fig. 4.

Survival curves for tumour cells irradiated *in vivo* in the absence (○) or presence of 1 mg/g Ro-07-0582 (●) and immediately plated and assayed *in vitro*. The data points and line for irradiations in the absence of the drug are redrawn from Fig. 3. The solid line through the points for irradiation in the presence of the drug was drawn assuming the effect of the drug was to decrease the D_0 for the hypoxic cells by a factor of 1.6. The dashed line was drawn for a factor of 2.1.

giving a D_0 of 2.6 Gy and an extrapolation number of 30. It is clear that clamping had a marked effect on the survival of the cells to radiation (Fig. 3). Clamping also reduced the scatter, so that it was possible to define the curve for tumours made hypoxic more accurately than that for unclamped tumours. By assuming a value for the oxygen enhancement ratio (o.e.r.) it is possible to estimate the fraction of the cells that were hypoxic as determined by this *in vitro* assay. Assuming a value of 2.7 for the o.e.r. (giving the dashed line in Fig. 3), the solid line through the points for cells irradiated in unclamped tumours was drawn assuming an hypoxic fraction of 5%. (In practice the calculated value of the hypoxic fraction is only weakly dependent on the value of the o.e.r. chosen.) The hatched area represents the region between hypoxic fractions of 2 and 15%.

Figure 4 shows the effect of the hypoxic cell sensitizer given to unclamped tumours at a concentration of 1 mg/g 30 minutes before irradiation. The measured survival values and the calculated line for an hypoxic fraction of 5% in normal tumours have been redrawn from Fig. 3 for comparison. The solid line through the survival values for irradiations in the presence of the drug was drawn assuming the effect of the drug was to decrease the D_0 of the survival curve for hypoxic cells by a factor of 1.6 (the enhancement ratio). The dashed line is for an enhancement ratio of 2.1; this value is probably too high to account for the observations (Fig. 4). Dose-modification was assumed because this is the mode of action of the drug *in vitro* (Asquith *et al.*, 1974).

In these calculations it has been assumed that the terminal slope of the survival curve for the naturally hypoxic cells is the same as that of the survival curve for artificially hypoxic cells (Fig. 3). In virtually all those tumours for which it has been possible to measure full survival curves (for example Barendsen and Broerse, 1969; Hill *et al.*, 1971; McNally, 1972) this has been found to be the case. Thus the lines drawn in Figs. 3 and 4 were calculated using only the eye-fitted line through the survival curve for clamped tumours (Fig. 3), the above assumption, with the additional assumption that the sensitizer only affects the D_0 to the survival curve for hypoxic cells.

In another series of experiments, tumours were excised at various times from one to 24 hours after irradiation and cell survival then assayed *in vitro*. The results of these experiments will be presented and discussed in the next section.

DISCUSSION

Assuming the TCD_{50} depends primarily on the radiosensitivity of the individual tumour cells, its high value (79.0 Gy), and the absence of a significant effect of clamping on the TCD_{50} (Fig. 1), suggest that the hypoxic fraction of cells in this tumour is very high, well over 50%. If this is the case, it follows that within the accuracy of any of the methods used for measuring tumour response, the effects of radiation on the rather small well oxygenated fraction should be barely detectable, *i.e.* the tumour would appear to respond as a uniformly hypoxic population. Thus, dose-effect curves based on tumour growth delay should not be expected to demonstrate the biphasic shape indicative of the presence of a comparatively small fraction of hypoxic cells, and the sensitizing drug Ro-07-0582 could be expected to act as a "dose-modifier" as discussed above, giving the same enhancement ratio as that measured using the TCD_{50} assay. Figure 2 shows that, as expected, the dose-effect curve for tumour growth delay was not biphasic, but that the Ro-07-0582 enhancement ratio was less than that measured by the TCD_{50} assay. Even though it was about two at the lowest dose of radiation used in the presence of the drug (10 Gy), a smooth curve representing a constant enhancement ratio of two did not fit the data. (The experimental point corresponding to the dose of 10 Gy in the presence of the drug was determined in a separate experiment whereas all the others were obtained concurrently.) The smooth curve shown in Fig. 2 gave an enhancement ratio of about 1.5, tending toward the value for the TCD_{50} assay at high doses. The enhancement ratio depended on the final size of the tumour chosen in the regrowth assay (Table I), but no matter what final size was chosen it was low at low radiation doses, increasing toward the TCD_{50} value at high doses.

While the regrowth assay does suggest a cell population with uniform radiation sensitivity, at lower X ray doses it does not give the same drug enhancement ratio as the TCD_{50} assay. It is possible that only at large doses of radiation do the lethal effects of the radiation on the cells dominate the response in this tumour, with its relatively large TCD_{50}, whereas at lower doses factors such as division delay and alterations in post-irradiation growth kinetics may be significant in determining the pattern of regrowth.

The results of the TCD_{50} assay would lead to the prediction that there should be little effect of clamping the tumour on the survival curve constructed from *in vitro* assays and that the sensitizer should be essentially dose-modifying. For both predictions this was clearly not the case (Figs. 3 and 4). The hypoxic fraction deduced from the cell survival curves was about 5% and the drug enhancement ratio was about 1.6 (instead of 2.1 as in the TCD_{50} assay).

Bearing in mind these discrepancies between the TCD_{50} and cell survival assays one can ask whether the measured survival curves would give a TCD_{50} of about 79.0 Gy. In order to calculate a TCD_{50} from the survival curves a number of assumptions have to be made. We assume:

(a) The cell survival curve at high doses has the form

$$S = ne^{-D/D_0} \quad . \quad . \quad . \quad (1)$$

where n is the extrapolation number

(b) A tumour recurs if one cell survives, the probability of curing an animal being given by $p = e^{-NS}$ where N is the number of cells in the tumour capable of repopulating it and S is the surviving fraction after a dose D Gy. If the tumour contains a fraction f of hypoxic cells, then for large single doses, at the TCD_{50}

$$p = 0.5 = e^{-fNS}$$

$$\therefore fNS = 0.69$$

Substituting for S from equation 1 and solving for D the TCD_{50}, gives:

$$D = D_0 \times \left[\log_e n - \log_e \frac{0.69}{fN}\right] \quad (2)$$

From the survival curves of Fig. 3, $D_0 = 2.60$ Gy, $n = 30$ and $f = 0.05$. The tumours were irradiated at a mean diameter of about 5.5 mm so that a reasonable value for N is probably between 10^8 and 10^9 cells per tumour. Taking these as the extreme values gives

$$49.91 \text{ Gy} \leqslant D \leqslant 55.89 \text{ Gy}$$

In other words, the survival curves do not predict the measured TCD_{50}. A value of N over 10^{12} would be needed to give a TCD_{50} of 79.0 Gy. Thus, the *in vitro* assay disagrees with the animal cure assay in regard to the hypoxic fraction, the drug enhancement ratio and the TCD_{50} value. There is, however, an explanation we wish to propose which can, in part, account for these discrepancies.

Effect of potentially lethal damage

For the cell survival assay the tumours were removed from the animals immediately after irradiation. It is possible that this rapid change in the cells' environment immediately after irradiation could affect their ability to survive the treatment. We therefore did a further series of experiments as indicated above, in which tumours were irradiated and excised at various times thereafter. Figure 5 shows the surviving fraction of cells assayed *in vitro* as a function of the time after irradiation that the tumours were excised. The doses were 15 Gy to unclamped tumours, a dose large enough to kill all the oxygenated cells so the survivors would have been hypoxic at the time of irradiation, and 19 Gy to clamped tumours in which normally well oxygenated cells would have been rendered hypoxic so they would not have been selectively killed. For cells from the clamped tumours there was no change in survival up to eight hours after irradiation (Fig. 5A). For cells from unclamped tumours ("naturally" hypoxic cells) there was a prompt increase in survival by a factor of about four within the first two to three hours, with probably little further increase in survival up to 16 hours later (Fig. 5B). This increase in survival represents recovery from potentially lethal damage (PLD) in the interval between irradiation and excision of the tumours (Hahn and Little, 1972; Little *et al.*, 1973). In this tumour this form of recovery was evidently restricted to cells that were naturally hypoxic rather than those made acutely hypoxic by the application of a clamp. If this were not the case one should also expect to see an increase in survival with time for cells from tumours that were clamped at the time of irradiation. As Fig. 5A shows, this was not the case.

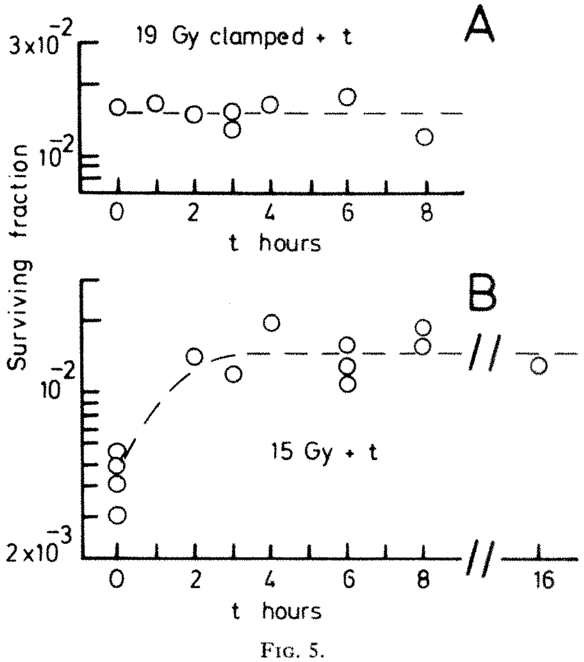

FIG. 5.

The surviving fraction of tumour cells assayed *in vitro* as a function of the time after exposure to a single dose of X rays at which the tumours were excised.

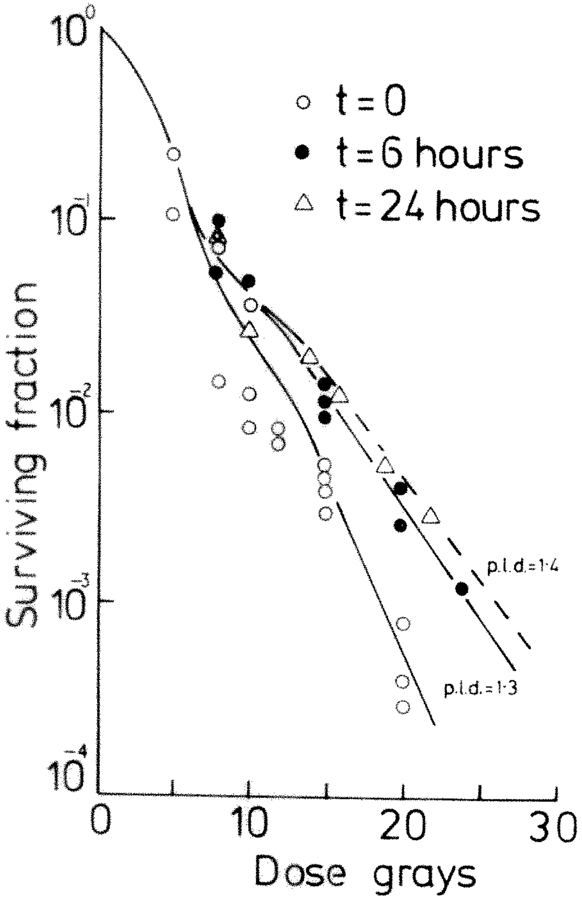

Fig. 6.

Survival curves for tumour cells from tumours excised immediately after irradiation (○) or six (●) or 24 (△) hours after irradiation. The lines through the six and 24 hour data points were drawn assuming the effect of recovery from PLD was to increase the D_0 for hypoxic cells by a factor of 1.3 or 1.4.

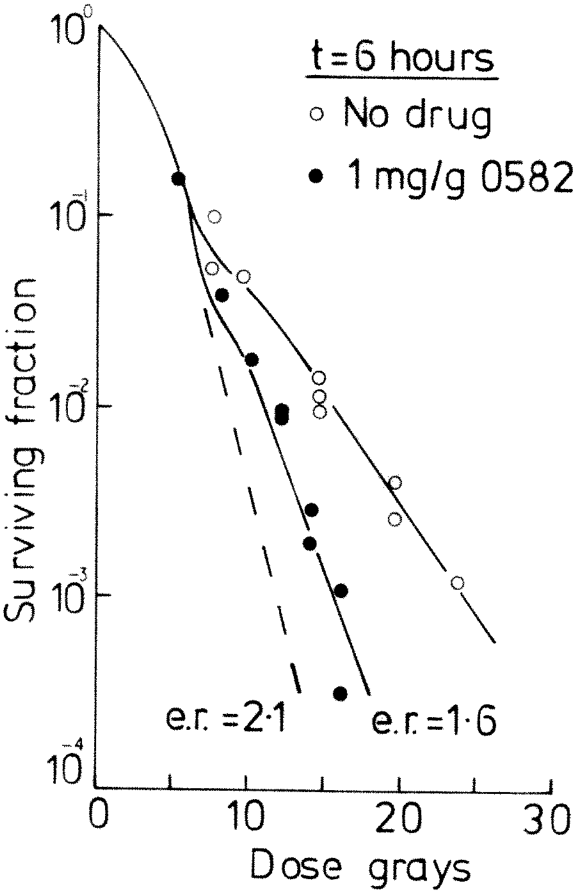

Fig. 7.

The effect of recovery from PLD on the enhancement ratio for Ro-07-0582. Tumours were excised six hours after irradiation in the presence or absence of 1 mg/g of the drug. The lines were drawn assuming a factor of 1.3 for recovery from PLD and drug enhancement ratios of 1.6 or 2.1.

Figure 6 shows the effects of recovery from PLD on the survival curves for cells from tumours irradiated in the absence of the sensitizer and excised six or 24 hours later. (The survival curve for cells from tumours excised immediately after irradiation is included for comparison.) The lines were drawn assuming the effect of recovery from PLD was to increase the D_0 for hypoxic cells by a factor of 1.3 from 2.6 Gy to 3.38 Gy, or by a factor of 1.4 to 3.64 Gy. The factor 1.4 probably represents an upper limit for the effect of recovery from PLD on the survival curve. This recovery had probably reached its maximum by six hours (Fig. 6). While it is possible to draw a line through the zero hour result, parallel to those for six and 24 hours, this is probably not valid for the reasons already given when the results shown in Figs. 3 and 4 were described.

Figure 7 shows the effect of recovery from PLD on the enhancement ratio for Ro-07-0582. The tumours were excised six hours after irradiation with or without injection of 1 mg/g of the drug. The lines were drawn assuming a factor of 1.3 for recovery from PLD and sensitizing enhancement ratios for the drug of 1.6 and 2.1. As Fig. 7 shows, it is clear that recovery from PLD occurred whether or not the sensitizer was present and did not affect the sensitizer enhancement ratio. The value of 2.1 is much too large to account for the observations.

The observation that only the naturally hypoxic tumour cells were capable of recovery from PLD, and not the oxic ones made hypoxic by a clamp, can explain the absence of an effect of a clamp on the TCD_{50} even though the hypoxic fraction was only 5%, if we can make the reasonable assumption that

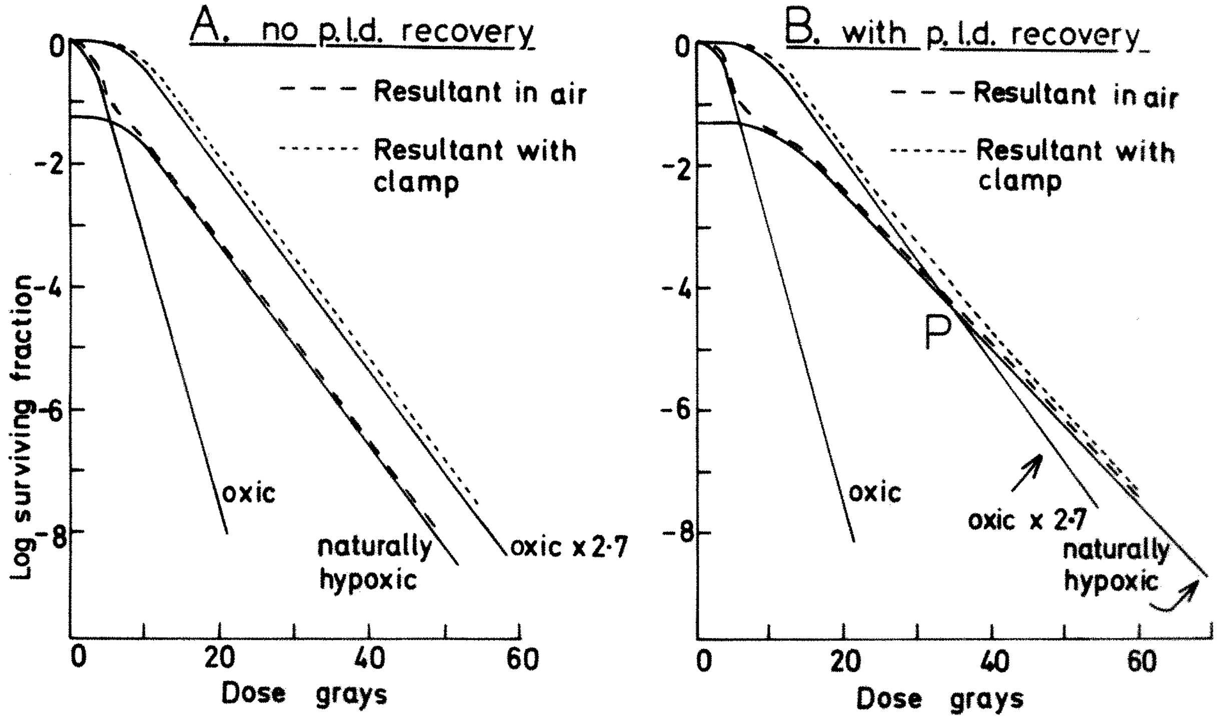

FIG. 8.

Theoretical survival curves for a mixture of oxic and hypoxic cells. The solid lines represent the survival curves for the separate components (oxic cells, naturally hypoxic, or oxic made hypoxic). The dashed lines represent the resultant survival curves obtained by adding the appropriate component curves. A is drawn assuming no recovery from PLD. B is drawn assuming that only the naturally hypoxic cells can recover from PLD. The lines have been drawn using experimentally determined survival curve parameters (see text).

the oxic cells would not have been able to recover from PLD even if the clamp had not been applied during irradiation. Figure 8 shows theoretical survival curves for a mixture of oxic and hypoxic cells. The survival curve parameters used to draw these curves were those derived from the results of the present experiments. Figure 8A shows the survival curves when the naturally hypoxic cells do not recover from PLD. The parameters used were: D_0 for hypoxic cells 2.6 Gy, oxygen enhancement ratio 2.7, survival curve extrapolation number 30, hypoxic fraction 5%. As Fig. 8A shows, application of a clamp displaces the resultant survival curve upwards relative to that for unclamped cells by an amount proportional to the hypoxic fraction. This displacement occurs at all levels of survival. In Fig. 8B, as well as being protected by hypoxia, the naturally hypoxic cells (but not the oxic ones) are assumed to be capable of recovery from PLD. The survival curve parameters are the same as in Fig. 8A except that the D_0 for the naturally hypoxic cell survival curve, relative to that for oxic cells made hypoxic, has been increased by a factor of 1.3 to 3.38 Gy, to allow for recovery from PLD. The resultant survival curve when a clamp is applied is obtained by adding the "oxic × 2.7" curve and the "naturally hypoxic" curve as in Fig. 8A, except that this time once survival is significantly less than that indicated by the point P (Fig. 8B), the survival curve for naturally hypoxic cells will dictate the response regardless of whether or not a clamp is applied. The presence of the clamp will only increase the dose of radiation beyond which the naturally hypoxic cells dominate the response (Fig. 8B). The value of the dose of radiation to give a surviving fraction represented by the point P in Fig. 8B can be calculated using the simple model already outlined. It will be determined by the equation

$$nfe^{-D/rD0}=n(1-f)e^{-D/D_0}$$

where r is the factor by which the D_0 for naturally occurring hypoxic cells must be increased over that for oxic ones made hypoxic by the clamp, due to recovery from PLD. For the survival curves shown in Figs. 4, 6 and 8B, D has a value of 35 Gy. Thus, since the TCD_{50} was 79.0 Gy, one would not expect it to be affected by clamping the tumours.

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Two discrepancies remain between the two (direct) methods of assaying cell survival (TCD$_{50}$ and *in vitro* assay). First, the enhancement ratio for Ro-07-0582 was larger in the TCD$_{50}$ assay (2.1) than in the cell survival assay (1.6); this difference is probably independent of recovery from PLD (Fig. 6). Second, the TCD$_{50}$ was much larger than the cell survival curves would predict. If we now allow for recovery from PLD so that the value for D_0 in equation 2 is increased by a factor 1.3 from 2.6 Gy to 3.38 Gy, then for values of N between 10^8 and 10^9 cells per tumour,

$$64.88 \text{ Gy} \leqslant D \leqslant 72.67 \text{ Gy}$$

This is still less than the measured TCD$_{50}$. A factor of 1.4 for the effect of recovery from PLD on the D_0, which probably represents an upper limit for the experimental observation (Fig. 6), would give a TCD$_{50}$ in the range 69.89 Gy to 78.29 Gy. The calculations of the TCD$_{50}$ based on equation 2 have assumed that all naturally hypoxic cells in the tumour are capable of repopulating it. This is unlikely to be the case, so that even assuming a factor of 1.4 for the effect of recovery from PLD, it is doubtful if the measured survival curves would predict the high TCD$_{50}$.

These discrepancies have, therefore, not been fully accounted for. The drug might be having more effect in the TCD$_{50}$ assay due to direct toxicity on the tumour cells. However, by six hours its concentration in the tumours will have become quite low (Flockhart, personal communication), and this time of contact with the cells did not affect the enhancement ratio measured *in vitro* (Fig. 7). Also, giving the drug after irradiation had no effect on the TCD$_{50}$, suggesting no cytotoxic action (Sheldon, unpublished data). The large TCD$_{50}$ could be due to a greater ability of the hypoxic cells in the tumour to absorb radiation damage as sublethal when left *in situ* than when plated in *vitro*. It is known that the degree of intercellular contact between cells *in vitro* can affect their ability to absorb sublethal damage (Durand and Sutherland, 1972).

It is clear from these results that the fate of irradiated cells in this tumour depends critically on the immediate post-irradiation environment. It follows that, without knowing the effects of this environment, incorrect interpretations of the results may be made. From a practical point of view it may not matter whether one assumes either that the hypoxic fraction is large or that the hypoxic cells are capable of recovery from PLD. However, in a fractionated course of radiotherapy, or in circumstances where drugs which could inhibit the cells' ability to recover from PLD are used in conjunction with radiation, the use of a single assay of radiation response alone could lead to erroneous conclusions. Without the use of several different methods of assay in the same tumour, the details of its radiation response, for instance the role of recovery from potentially lethal damage, may not be elucidated.

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Absorbed doses in the marrow during ^{131}I therapy

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ABSTRACT

Absorbed doses to red marrow and blood from ^{131}I therapy have been re-evaluated using data which has become available more recently. Uncertainties in the calculations are discussed and a comparison is made with previously published dose estimates. The mean dose to red marrow from the treatment of hyperthyroidism is estimated to be 0.59 rad mCi^{-1}, compared with 0.36 rad mCi^{-1} for the euthyroid state.

Studies of leukaemia incidence in patients treated with ^{131}I for either hyperthyroidism or thyroid carcinoma have been made in order to determine whether there is any increase in incidence as a result of treatment and, if so, the magnitude of the risk of leukaemia induction per rad to the bone marrow. Studies of this type have been reviewed in the 1972 UNSCEAR report (UNSCEAR, 1972), which indicates some uncertainty as to the magnitude of the marrow doses and the ratio of marrow to blood dose. Absorbed doses to red marrow and blood from ^{131}I therapy have been re-assessed taking account of data which have become available more recently.

METHOD OF CALCULATION

Estimates of rates of uptake, metabolism and excretion of radioiodine in the treatment of hyperthyroidism, thyroid ablation and thyroid carcinoma have been provided by Pochin and Kermode (1975). Mean accumulated activities in various body organs taken or derived from their data are listed in Table I. Following McEwan (1974a) the accumulated activity in blood was taken as 0.3 times the extra-thyroidal inorganic iodine plus 0.25 times the extra-thyroidal protein bound iodine activity. It is to be noted, however, that there is considerable variation in the literature in the size of the extra-thyroidal iodine spaces. Extra-thyroidal iodine not in blood or marrow was considered to be uniformly distributed throughout the body. Accumulated activities in the bladder were estimated following methods also described previously (McEwan, 1974a and 1975), and accumulated activities in the red marrow as described below. Data for a normal thyroid (25% uptake) have been added for comparison in Table I from McEwan (1974a).

For penetrating radiations from each of the source organs listed in Table I, doses to red marrow and blood have been calculated using specific absorbed fractions and organ masses tabulated in the ICRP Report 23 (ICRP, 1975) and data on equilibrium absorbed dose constants of the component radiations calculated by Dillman (1969). The dose contribution to blood from non-penetrating (np) radiation emitted from radioiodine in blood has been calculated using an absorbed fraction of 0.82 (McEwan, 1974b). The dose contribution to marrow from np radiation in blood was estimated assuming that the blood in marrow was uniformly distributed in fine capillaries in which the absorbed fraction was very small. A mean absorbed fraction of 0.79 in trabecular marrow for a uniform distribution of ^{131}I within it was derived from the β ray dose factors for trabecular bone of Whitwell and Spiers (1976) following the method of Spiers *et al.* (1976). It may be noted that a factor of 0.79 had been estimated more than 20 years earlier by Robertson and Godwin (1954). A recent approximate calculation gave a value of 0.76 (McEwan, 1976). One of the greatest sources of error in estimating absorbed doses in red marrow arises from the uncertainty in the concentration of radioiodine in marrow. Robertson and Godwin (1954) assumed a marrow to blood concentration

TABLE I

MEAN ACCUMULATED ACTIVITIES IN BODY ORGANS (mCi-d/mCi ADMINISTERED)

Organ	Normal	Hyperthyroidism	Thyroid ablation	Thyroid carcinoma
Stomach	0.02	0.02	0.02	0.02
Thyroid or tumour	2.72	4.70	1.20	0.17
Blood	0.15	0.23	0.15	0.23
Red marrow	0.03	0.04	0.03	0.04
Remainder of body	0.35	0.62	0.37	0.51
Bladder	0.08	0.03	0.08	0.10

TABLE II

Mean doses to red marrow and blood from ^{131}I (rad mCi^{-1})

Source organ	Normal		Hyperthyroidism		Thyroid ablation		Thyroid carcinoma	
	Red marrow	Blood	Red marrow	Blood	Red marrow	Blood	Red marrow	Blood
Stomach	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Thyroid/tumour	0.157	0.236	0.272	0.408	0.070	0.104	0.101	0.015
np in marrow or blood	0.132	0.222	0.204	0.334	0.132	0.222	0.203	0.340
Remainder of body*	0.064	0.051	0.107	0.086	0.066	0.053	0.094	0.075
Bladder	0.008	0.011	0.003	0.004	0.008	0.011	0.009	0.012
Total	0.36	0.52	0.59	0.84	0.28	0.39	0.32	0.44

*Includes penetrating radiation contribution from blood and marrow.

ratio of 1.0. The blood content of red marrow is about 6% by weight (ICRP, 1975) so that a concentration ratio of 1.0 implies an appreciable uptake of ^{131}I into marrow tissue. Very little data appears to be available on this point although a report of necropsy studies on four patients who had received ^{131}I two to 21 days before death gave a concentration ratio of 0.62 (Trunnell *et al.*, 1950) which was a value used by Lewallen (1963). In the absence of confirmatory data this value is also used here. It may be noted that a concentration ratio of about 0.7 is implied if the concentrations in erythrocytes and red marrow are similar, and the concentration in red cells is about half that of blood plasma (McEwan, 1974a).

Results

Calculated mean dose contributions to red marrow and blood are listed in Table II. The doses are applicable only to average single treatments, and wide variations from the mean are possible, particularly in the blood doses resulting from treatments of thyroid carcinoma. For the latter a treatment régime may comprise an average of six treatments of about 150 mCi each over a period of three years (Pochin, 1967), and the blood dose resulting from the first treatment of such a series may be much greater than that from subsequent treatments. In calculating the mean doses from treatments of thyroid cancer the tumour has been assumed to be in the same position as the thyroid.

In the case of thyroid cancer treatments the mean calculated dose ratio of 0.73 red marrow to blood may be compared with previous estimates of 0.8 (Robertson and Godwin, 1954) and 0.44 (Lewallen, 1963). The value obtained is very dependent upon the choice of the marrow to blood concentration ratio. For a course of six treatments of 150 mCi each the doses calculated here indicate a total red marrow dose of about 290 rad and a total blood dose of about 400 rad.

In the case of treatments for hyperthyroidism the mean calculated marrow to blood dose ratio is 0.70 which may be compared with the estimate of 0.46–0.86 made by Saenger *et al.* (1968). In their study mean blood doses were estimated at about 1.2 rad mCi^{-1} and bone marrow doses at 0.8–1.5 rad mCi^{-1}, whereas Green *et al.* (1961) obtained values of 1.7 rad mCi^{-1} and about 1.4 rad mCi^{-1} respectively. The mean blood dose calculated in this paper is 0.7 times that used by Saenger *et al.* and only 0.35 times that of Green *et al.* Assuming the validity of the data of Pochin and Kermode (1975), the greatest uncertainties in the mean doses given in Table II arise from the selection of the appropriate fractions of inorganic extrathyroidal iodine in blood, and the appropriate ratio of the ^{131}I concentration in red marrow to that in blood. This ratio has been assumed constant with time, but further study of these values would be useful. Since, however, for the hyperthyroid case, about 60% or more of the doses to blood and marrow arise from gamma radiation, principally from the thyroid, a major adjustment of the values used here would be unlikely to result in modification of the calculated doses by more than about 25%.

A mean dose of 0.59 rad mCi^{-1} to the red marrow implies an average dose to marrow of 5.3 rad for leukaemia patients of Saenger *et al.* and 6.3 rad for the patients without leukaemia. Based on data from Japanese bomb survivors and ankylosing spondylitics (UNSCEAR, 1972), and assuming a linear dose-effect relationship, these doses appear to be too small to allow a demonstration of an excess risk of leukaemia from radiation in patients treated with ^{131}I in Saenger *et al.*'s series. Tompkins (1970) has suggested that no excess leukaemia has in fact been demonstrated in exposed adult populations receiving doses below about 80 rad, although a recent report tends to refute this (Pochin 1976).

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Book review

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With the changes arising from the Health and Safety at Work Act and the European Council Directive on basic safety standards for protection against ionizing radiation, any guidance that enables the ICRP permissible dose limits to be interpreted in legislation and instrument design would be welcome. In this respect the latest ICRU report on dose-equivalent and dose-equivalent index is timely. However, although the report is a considerable aid to the understanding of these concepts, and introduces two new ones to be known as the deep and shallow dose-equivalent indices, it is not entirely clear how these concepts will be applied. Indeed, it seems likely that considerable discrepancies will exist between what monitoring instruments measure and what they purport to measure. Some of the reasons for these discrepancies are acknowledged and discussed in the report.

Everyone with an interest in radiological protection should read the report, which leaves one with the expectation that ICRU will have to make further attempts to bridge the gap between radiological protection practice and the concepts of ICRP.

J. A. DENNIS.

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A versatile and economic whole-body counter based on liquid scintillation detector modules

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ABSTRACT

A whole-body counter comprising rectangular liquid scintillator detector modules is described. Photomultipliers are used economically and the use of local shielding leads to a further reduction in cost. In conjunction with a moving bed, the modular arrangement provides a versatile system which allows high sensitivity static counting using all detectors, or scan counting using selected combinations of detectors. The total body potassium content of a standard man (140 g K) can be estimated with a statistical counting error of 2.2% in a counting time of 1000 seconds. Methods of using the counter for total body potassium and gastro-intestinal absorption measurements are presented.

Liquid scintillators were first applied to whole-body counting by Anderson *et al.* (1956) using the Los Alamos counter, Humco I. This counter clearly demonstrated the value of liquid scintillator for high sensitivity counting, and a number of 4π and 2π counters based on the Humco cylindrical design are now in existence (*Directory of Whole-body Radioactivity Monitors*, 1970). The difficulty of collecting scintillation light from such large counters is, however, a problem which limits their performance and resolution unless many photomultipliers are used. In this respect, the development of large area rectangular whole-body counters by Barnaby *et al.* (1967) was important in showing that the use of internal reflection makes possible good light collection efficiency with considerable economy in the number of photomultipliers required.

With all large counters, of course, there is the additional burden of expensive shielding, and in view of this it is somewhat surprising that liquid scintillator, with its proven versatility, has not been more fully exploited for the development of whole-body counters of simpler, cheaper design. This paper describes the design and properties of such a counter which combines the advantages of both scanning and high sensitivity counting. Particular attention has been paid to the efficient collection of scintillation light with a minimum of photomultipliers, and for this reason the rectangular design has been used. However, in contrast to large detectors viewed by several photomultipliers (Barnaby and Jasani, 1968), smaller modules are used, each viewed by a single photomultiplier. This leads to practical as well as economic advantages.

DESCRIPTION OF THE COUNTER

The counter consists of eight identical detector modules (Fig. 1). Each module, in the form of a double-compartment rectangular Perspex box ($80 \times 20 \times 17$ cm), contains 17 litres of an inexpensive scintillator fluid (Barnaby and Jasani, 1966) with a high flash point (50°C). The smaller compartment (20 cm long) filled with medicinal paraffin separates the scintillator from the single photomultiplier (EMI 9623A), and magnesium oxide powder contained in thin-walled Perspex envelopes is used as reflector at all other surfaces of the Perspex tank. Only 3.3% of the total surface area of the module is occupied by the photocathode and, to allow this economy, special attention has been paid to the efficient collection of scintillation light. Details of the design and properties of a detector module have been described previously (Smith, 1976).

Pairs of modules are placed side by side in each of four identical light-tight boxes made of aluminium alloy which are placed two above and two below a movable bed (Fig. 2). The long axes of the modules are perpendicular to the long axis of the bed, with the scintillator sections symmetrically disposed about the mid-line of the bed. Thus the sensitive region of the counter extends 106 cm along the bed and 60 cm transversely, the upper and lower detectors being separated by 50 cm. The four metal boxes are supported on a steel framework by means of roller

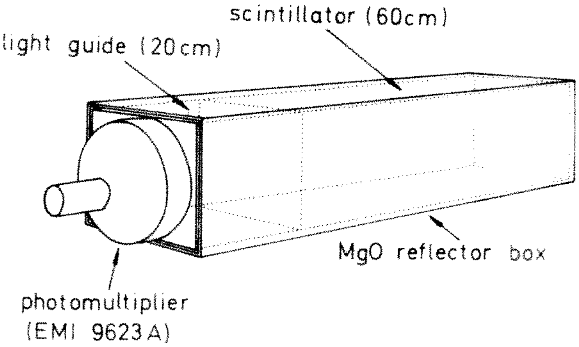


FIG. 1.
A single liquid scintillator detector module.

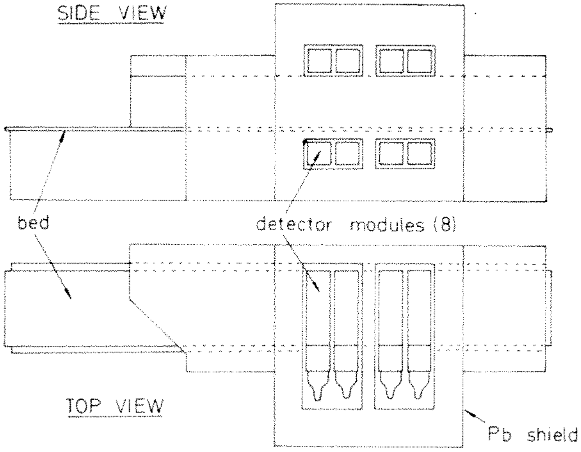


Fig. 2.
Side elevation and top view of the eight-module whole-body counter.

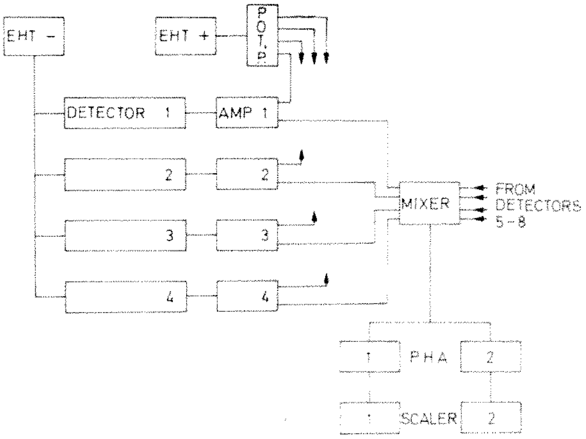


Fig. 3.
Block diagram of whole-body counter electronics.

bearings which facilitate removal of the detectors for maintenance. The framework also provides support for the local lead shielding. A bed (190×60 cm), mounted 56 cm above the ground on an independent aluminium alloy framework, can be motor driven between the upper and lower detectors at selected constant speeds or manually positioned anywhere along the traverse. The framework of the bed is extended at the entrance of the counter to allow easy access for patients. The extent of movement of the bed is such that its centre position can traverse between positions 222 cm in front of and 52 cm beyond the centre of the detector region. This allows high sensitivity counting using all eight detectors in conjunction with moving or stationary bed geometries, or scan counting using selected combinations of detectors.

The counter has been constructed alongside a 15 cm thick steel cubicle which therefore constitutes the shielding wall (260 cm long) for one side of the counter. Elsewhere, local shielding is provided by lead bricks to a thickness of 10 cm in the immediate region of the detectors and reducing to 5 cm at ports at either end of the counting compartment. Patients enter and leave the counter at the same port and a 5 cm lead screening wall is placed 30 cm from the end of the opposite port. Both ports remain open during counting.

The counting compartment is 65 cm wide and 36 cm high and lined with polished aluminium sheet. Music is available during the counting period, but the use of an open ended counting chamber is probably the most significant anticlaustrophobial measure incorporated.

The electronic system used with the counter is shown schematically in Fig. 3. The photomultipliers (EMI 9623A) were specially selected for low dark current, typical values being 20–60 nA at an overall tube gain of 200 amp lumen^{-1}. Two EHT units (one +ve and one −ve) supply each bank of four photomultipliers, the first dynodes being earthed and the cathodes operated at −750 V. Positive EHT can be varied by means of two four-way potentiometer units and final adjustment is made by variable-gain charge-sensitive amplifiers. Pulses from the eight detectors are mixed and the final output shared between two single-channel analysers and scalers. Choice of detector combinations is effected by appropriate connection to the eight-way mixer unit. The timer unit may be operated manually or by means of magnetic reed switches placed along the traverse of the couch.

The use of a single photomultiplier with each detector facilitates balancing of gain of the eight detectors since there is no sharing of scintillation light (Smith, 1976). This procedure is performed daily by connecting each detector in turn to a 128-channel analyser and adjusting the amplifier gain to locate the Compton peak of a ^{137}Cs source in predetermined channels.

Properties of the Counter

Background

Integral and differential background spectra obtained with the counter are shown in Fig. 4. In the energy region 0.3–2.0 MeV the background count rate is 300 counts sec^{-1}, equivalent to 2.3 counts sec^{-1} l^{-1} of scintillator. Most of the counts above 2 MeV, as shown in the integral spectrum, arise from cosmic rays which produce very large pulses

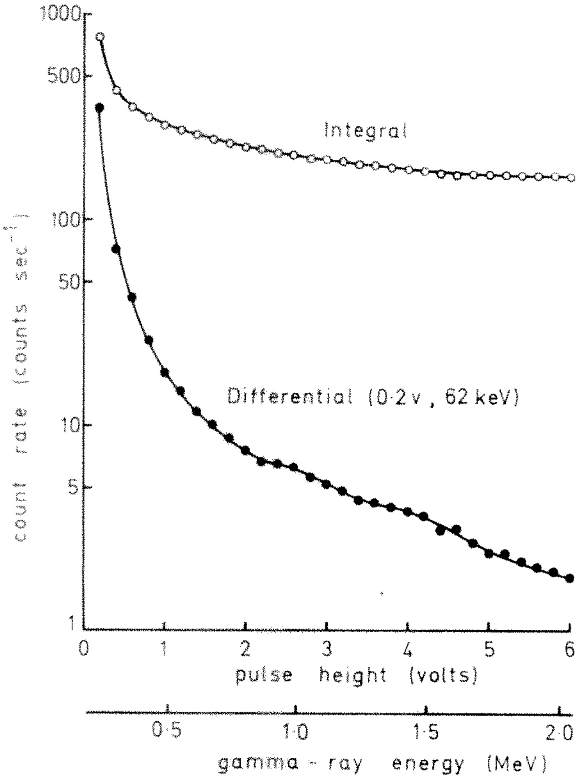


Fig. 4.

Integral and differential background spectra. The differential spectrum represents counts per channel of 62 KeV width.

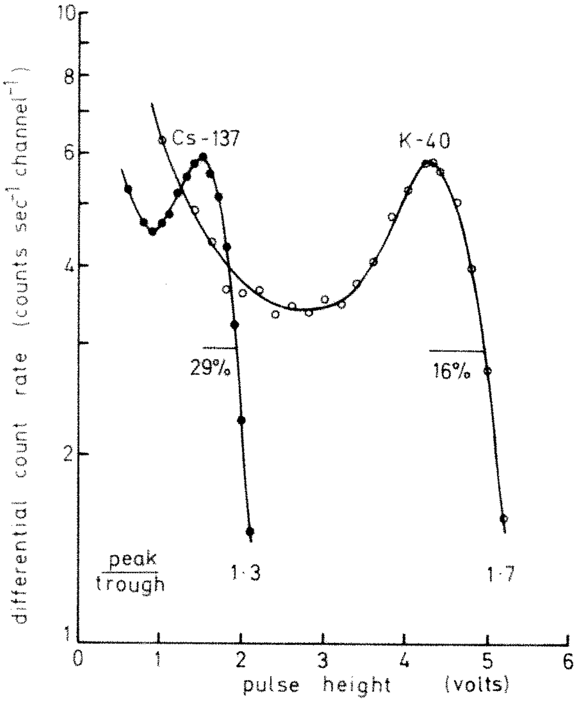


Fig. 5.

Compton spectra of ^{137}Cs and ^{40}K obtained using complete counter. Half resolution values and peak-to-trough ratios are shown.

due to the large volume of scintillator. Backgrounds in the upper and lower banks of four detectors are not significantly different. The effectiveness of the shield was determined by observing background spectra with a combined pair of detectors inside and outside the shield and also inside a 15 cm thick steel cubicle (Nuclear Enterprises). The background reduction factor in the energy region 0.3–2.0 MeV obtained with the local shield was 21 compared to 29 inside the steel cubicle. In the ^{40}K counting channel (1.06–1.90 MeV) the factors were 17.4 and 21.8 respectively. Inherent radioactivity present in a pair of detectors and their metal container was investigated using eight NaI detectors (10 cm dia. × 7.5 cm) inside the same steel cubicle. The spectrum showed peaks at 1.46 MeV (^{40}K) and 0.61 MeV (RaC). Less distinct peaks were observed at about 0.23, 0.35 and 2.2 MeV, all presumably due to radium daughters although the latter peak may be due in part to the interactions of cosmic ray neutrons with H atoms in the scintillator to yield 2.23 MeV γ-rays (Rundo and Bunce, 1966). A number of materials from which the detectors and shield were made were measured for radioactive content using the 8-NaI detector counter. No significant radioactive contamination was detectable in the aluminium components of the detector boxes, in the steel girder sections used for the shielding framework, in the Perspex tanks or in the liquid scintillator. However, clear evidence of the presence of potassium and radium in the photomultipliers was obtained and it is concluded that the photomultiplier is the major source of inherent radioactivity in each detector.

Energy resolution and linearity

Spectral resolution of the combined eight detectors (Fig. 5) is certainly adequate to allow the Compton peak of ^{40}K (1.46 MeV) to be counted to the exclusion of ^{137}Cs γ-rays (0.661 MeV). Half-resolutions (half width of the Compton peak at half height, measured on the high energy side) of ^{40}K and ^{137}Cs are 16% and 29%, respectively. For individual detectors, typical values are 14% and 26% respectively (Smith, 1976).

Pulse-height spectra of a number of radionuclides which emit γ-rays in the range 0.32–1.52 MeV are

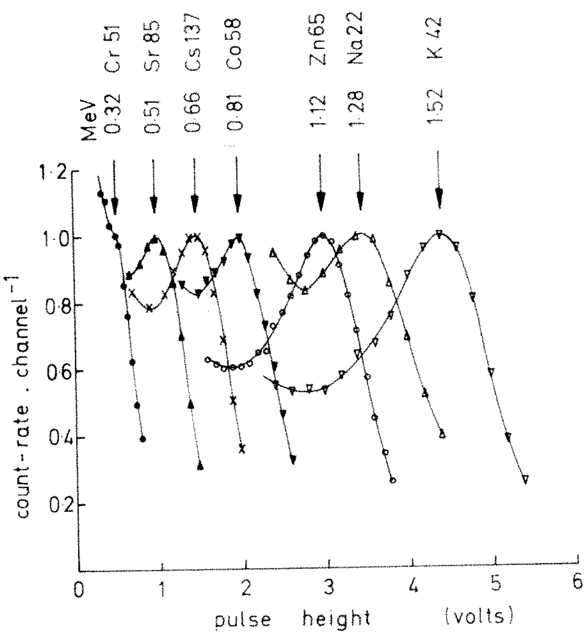


FIG. 6.

Spectra of various γ-ray emitting radionuclides.

shown in Fig. 6. Spectra were obtained with each source placed at the centre of the counter. There is an excellent linear relationship between peak pulse height and maximum energy transfer in a first Compton collision, and the intercept on the energy axis (0.045 MeV) is similar to that observed in other studies (Burch, 1961).

Counting geometry

The combination of modular detectors and a moving bed provides for various options of counting methods permitting the appropriate choice for a given application. For example, when highest sensitivity is required all eight detectors are used, but in situations where lower sensitivity can be tolerated the use of a scanning procedure with fewer detectors reduces the undesirable effects of nonuniform distribution of radioactivity.

A point source of ^{137}Cs in air was used to investigate the variation in counting efficiency with displacement of the source along the longitudinal, transverse and vertical axes of the counter for each of a number of possible counting methods. The methods are listed below and illustrated in Fig. 7.

(a) Scan-counting method 1. All eight detectors were operational and the bed scanned at constant speed between the detectors, through a distance of 102 cm.

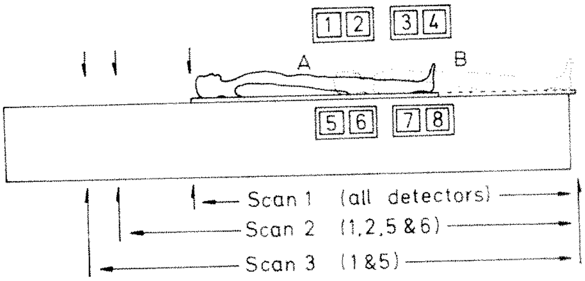


FIG. 7.

Diagram showing four different methods of counting. Scans 1, 2 and 3 are used with 8, 4 and 2 detectors respectively. Positions A and B are used in the stationary counting method.

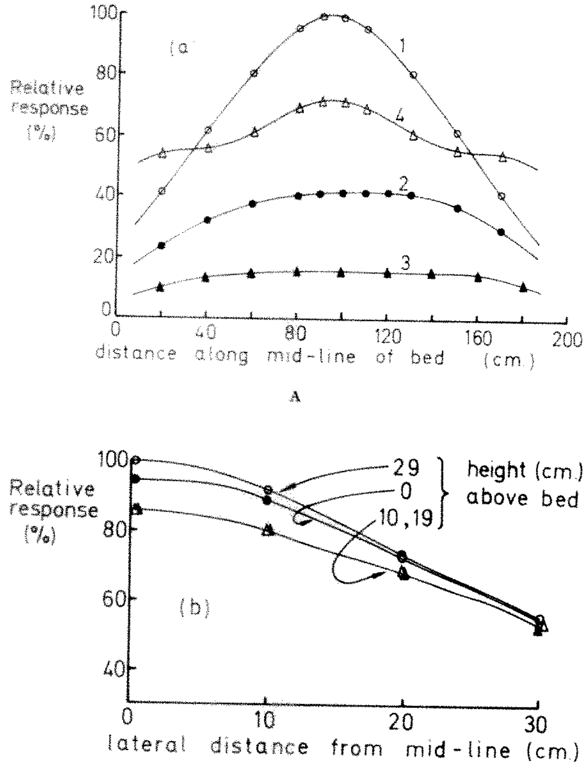
(b) Scan-counting method 2. Only detectors 1, 2, 5 and 6 were operational and the scan length was 160 cm.

(c) Scan-counting method 3. Only detectors 1 and 5 were operational and the scan length was 185 cm.

In the above three methods, the scans were symmetrically disposed about the centre of the detector combination used and scans were made in both directions. Scan lengths were limited by the end stop at the exit of the counter and thus increased through methods 1 to 3.

(d) Stationary counting method 4. With all eight detectors operational, measurements were made with the bed placed in turn at each of two positions (A and B) symmetrically disposed about the centre of the counter, and the count rates were added. A number of different combinations of pairs of positions were investigated.

Counting efficiency variations along the three axes of the counter are shown in Fig. 8. Method 1 is very sensitive to source location on the longitudinal axis as a result of the limited scan length relative to the effective detector length. As expected, the response becomes increasingly more uniform as the scan length increases but, in the present system, this can only be achieved by reducing the number of operational detectors. Of various combinations of pairs of counting positions tried in Method 4, the response shown in Fig. 8 is that obtained for the two positions at the start and end of the scan used in Method 1. Although flatter responses were obtained with other combinations, this pair was chosen because it produced the most uniform response to different sections of a standard 68 kg polythene phantom filled with KCl solution (Table I). Apparently the slightly increased geometric efficiency compensates for increased attenuation in the fatter abdominal region of the phantom.



A

B

Fig. 8.

Response to a ^{137}Cs point source in air in three perpendicular axes.

(A) Variation in longitudinal axis for counting methods 1 to 4 as indicated.

(b) Variation in transverse and vertical axes for all counting methods.

TABLE I

Counting efficiencies (Method 4) for different sections of a 70 kG KCl phantom

Section	Counts sec^{-1} gK^{-1}
Head and neck	0.089
Trunk	0.090
Abdomen	0.105
Arms	0.096
Thighs	0.104
Legs	0.093
Complete phantom	0.097
Range*	±8.3%

* Range of differences in values between individual sections and the complete phantom.

Method 4 also compensates to a certain extent for errors in positioning a subject in the longitudinal axis. A 5 cm displacement of the KCl phantom in this axis resulted in a change in count rate of less than 1%.

Using a 68 kg KCl phantom the count rate obtained in the upper detectors was 82.4% of that in the lower detectors, but increased to 96% with a 96 kg phantom of the same length.

Counting efficiency and sensitivity

The thickness of the scintillator (17 cm) is approximately equal to one attenuation length for 1.5 MeV γ-rays. Gamma-ray counting efficiencies for various commonly used radionuclides, distributed in a uniform anthropomorphic phantom, have been measured for the four different counting methods outlined above (Table II). Energy bands were chosen to include the Compton peaks of the various radionuclides. Counting efficiencies for the non-scanning technique (Method 4) are about 3%, and the efficiencies of Methods 1 to 4 are in the approximate ratios 5 : 2 : 1 : 4. Using Method 4, the minimum detectable activity of a 100% γ-emitter, which produces a count in 1000 seconds equal to three times the standard error of the background count, is about 0.6 nCi. The minimum activity measurable with a statistical counting error of 5% in 1000 seconds is about 6 nCi.

Stability

The procedure of balancing gains of the eight detectors leads to a high degree of stability of counting efficiency. Variations in gain due to temperature fluctuations are largely reduced by having the minimum ambient room temperature controlled at 21°C. In 119 measurements of a standard KCl phantom during a period of 12 months the standard deviation of the potassium counting efficiency was only 0.8% of the mean. Over the same period, measurements of background, using a water phantom, have shown long-term variations which exceed the variations expected from counting statistics. The standard deviation of 119 measurements was 1.4% compared to the counting statistical standard error of 0.53%. However, the day by day background stability is satisfactory. Long-term background variations have been observed by other workers (Poretti *et al.*, 1967).

Use of the Counter

Total body potassium (TBK) estimation is expected to be the main application of the whole-body counter and the dual stationary position counting

TABLE II

COUNTING SENSITIVITY'S (COUNTS SEC^{-1} μCi^{-1}) AND EFFICIENCY, E (%) FOR VARIOUS RADIONUCLIDES DISTRIBUTED IN A 70 kg PHANTOM, FOR FOUR DIFFERENT COUNTING METHODS

Radionuclide	Method 1		Method 2		Method 3		Method 4				
	S	E	S	E	S	E	S	E	B	MDA (nCi)	MMA (nCi)
^{51}Cr	131	3.9	61	1.84	25	0.76	105	3.2	136	10.5	100
^{131}I	1155	3.9	539	1.84	222	0.76	933	3.2	113	1.1	10
^{137}Cs	1022	3.2	476	1.13	197	0.61	825	2.6	75	1.0	9.6
^{58}Co	1674	3.8	700	1.35	322	0.73	1352	3.1	68	0.6	5.6
^{59}Fe	1360	3.6	481	1.27	262	0.70	1100	2.9	62	0.7	6.6
^{60}Co	2644	3.6	936	1.27	509	0.69	2136	2.9	70	0.4	3.6
^{22}Na	1225	3.3	434	1.17	236	0.64	990	2.7	46	0.7	6.3
^{42}K	242	3.6	86	1.27	47	0.70	196	2.9	48	3.4	33
^{40}K	0.12*	3.6	0.056*	1.27	0.023*	0.70	0.097*	2.9	49	6.8†	67†

MDA = Minimum detectable activity (3 × standard error of background in 1000 sec)
MMA = Minimum measurable activity (statistical counting error of 5% in 1000 sec)
B = Background count rate (counts sec^{-1})
* = Counts sec^{-1} gK^{-1}
† = gK

method has been adopted for this purpose. Whole-body radioactivity is measured for 500 sec in each position and the two counts are summed. A background phantom (68 kg) filled with distilled water is similarly measured before and after the subject and the background applicable for the subject is derived from this measurement modified by a factor appropriate for his weight. This factor is interpolated from a calibration curve obtained with a range of water phantoms. A daily check is made of the ^{40}K counting efficiency using a standard KCl phantom (68 kg) containing 1400 g K. The subject's TBK is calculated using a calibration factor (counts sec^{-1} gK^{-1}) determined from his height and weight. The counter has been calibrated by the administration of ^{42}K to groups of male and female subjects covering a wide range of weights using the method described by Burkinshaw (1967). Regressions of calibration factors on various functions of height and weight were investigated, and the least standard deviation from regression resulted from the use of the parameter (weight height^{-1})$^{\frac{1}{2}}$. The potassium counting efficiency for a standard 70 kg man is about 0.1 counts sec^{-1} gK^{-1} with a background of 48 counts sec^{-1}. The statistical counting error on a measurement of 140 gK is, therefore, 2.2% and the error on an absolute measurement is 3.2% when a calibration factor is interpolated from regression.

TABLE III

REPRODUCIBILITY OF TOTAL BODY POTASSIUM (TBK) MEASUREMENTS ON AN INDIVIDUAL (STATISTICAL COUNTING ERROR OF INDIVIDUAL MEASUREMENTS = 2.5%)

	TBK (g)	Mean ± S.D.	Excess* coefficient of variation
6 measurements on one day	122.6 124.4 121.0 127.7 123.5 121.3	123.4 ± 2.5 (2.0%)	0
10 measurements over three months (maximum weight change = 0.8 kg)	122.1 122.7 128.9 122.2 118.8 126.9 117.1 122.1 122.4 122.5	122.6 ± 3.4 (2.8%)	1.5%

* In addition to statistical counting error.

The reproducibility of the counter for potassium estimations has been verified by making repeated measurements on a subject on one day (the subject being repositioned in the counter on each occasion) and also over a period of three months during which time there was little change in his weight (Table III). The statistical counting error of the subject's estimated TBK was 2.5%: the standard deviation of six measurements on one day was 2.0% and of ten measurements over three months was 2.8%. The latter value indicates a coefficient of variation of 1.5% in addition to that due to counting statistics, which presumably reflects real changes in TBK occurring during that time. Studies are presently being made to compare TBK values measured both with this counter and with our multiple NaI crystal whole-body counter: results of more than 90 comparisons made so far indicate excellent agreement. These investigations will form the basis of a subsequent report.

The scanning method using four detectors (Method 2) is used to measure absorption of oral doses of ^{58}Co-labelled vitamin B_{12} (0.5 μCi) and of ^{59}Fe (1 μCi). Whole-body radioactivity is measured one hour after administration of the dose to establish the 100% retention value. The sensitivity of this counting method is such that 10% retentions of these radionuclide doses can be measured with a statistical counting error of about 2% in a scanning time of 204 sec. For six subjects with absorptions of ^{58}Co-vitamin B_{12} in the range 3 to 62%, retentions were estimated both by whole-body counting and by analysis of faecal radioactivity. There was good agreement between the methods, the mean difference being 3.6% of the administered radioactivity. There was also generally good agreement between absorption values measured by the present counter and by our NaI crystal counter. The values obtained by photopeak counting with the NaI counter, however, slightly exceeded those obtained with the liquid scintillation counter. In 17 comparative estimations of absorption of ^{58}Co-vitamin B_{12} the mean difference was 3.3 ± 0.7 (SEM) % of the administered dose ($p < 0.001$). This result presumably reflects changes in calibration factors due to redistribution of the radionuclide over the period of measurement. The scanning method was chosen in order to reduce this effect in this type of study.

CONCLUSIONS

Some relevant design details and performance data for the present counter can be compared with those of other large volume liquid or plastic scintillator counters listed in the *Directory of Whole-body Radioactivity Monitors* (1970). The resolution of the present counter compares favourably with the best published values despite its low value of photocathode coverage (3.3%). For example, in the Los Alamos counter (Humco II) the ^{40}K and ^{137}Cs half resolutions of 18% and 25% respectively are similar to those of the present counter, but photomultipliers cover 21% of the surface area of the counter. Other counters utilizing rectangular detectors, usually of plastic scintillator, have comparable resolutions but photocathode coverage values are mostly in excess of 5%. These results emphasize the importance of designing detectors for efficient light collection.

The ^{40}K counting channel used with the present counter is made as wide as possible, the lower discriminator being set where contributions from the ^{137}Cs spectrum first appear in this channel. The effect of the presence of 1 nCi ^{137}Cs in the body is equivalent to less than 0.04 g K. In contrast, some counters have such poor resolution, even though they use additional photomultipliers with larger dimensions, that there is considerable breakthrough of counts due to ^{137}Cs in the ^{40}K counting channel. This complicates TBK estimations and reduces their accuracy.

The present counter uses a total scintillator volume of only 135 litres, which represents 9 to 26% of the volumes used in 4 π annular liquid scintillator whole-body counters listed in the *Directory of Whole-body Radioactivity Monitors*. However, despite its low counting efficiency compared with most annular counters, its sensitivity is adequate for routine TBK measurements with a counting period of 1000 seconds.

The relatively small detector volume and the arrangement of the detectors allow the use of local shielding. In addition, the small number of photomultipliers and the use of a cheap scintillant afford considerable economy in the present design. We have not explored the possibility of using photomultipliers made from low radioactivity glass. Their use would undoubtedly be advantageous, but probably unwarranted in view of the counting sensitivity achieved with the present system.

The scanning facility, together with the option on the number of detectors used, makes for a versatile counter suitable for measuring a wide range of radioactivity, equivalent to 6 nCi to 15 μCi of a 100% γ-emitter. The combination of different counting methods permits measurements of retentions of administered radionuclides over long periods. Also important in this respect, the good resolution of the counter ensures that some clinically useful radionuclide combinations, for example, ^{57}Co and ^{58}Co; ^{59}Fe and ^{51}Cr; ^{47}Ca and ^{47}Sc, can be satisfactorily studied. The counter described is proving to be a valuable complement to our multi-crystal whole-body counter but it clearly is a useful instrument in its own right, capable of meeting the requirements of all but the most sophisticated of multi-isotope clinical studies. It is hoped that this paper will stimulate wider exploitation of liquid scintillator modules for bulk sample and whole-body counters.

ACKNOWLEDGMENTS

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Book review

NCRP Report No. 47. Tritium Measurement Techniques. pp. v+97, 1976 (National Council on Radiation Protection and Measurements), Washington D.C. $4.50.

This recent addition to the useful NCRP report series was prepared by a committee of leading American experts in the field. The report progresses through the various stages involved in tritium analysis, with sections on sample collection, sample preparation, measurement techniques and finally standardization and calibration. The introductory parts are very brief and obviously assume a knowledge of the context and need for special tritium measurement techniques. For example, at the beginning of the sample collection section, it is stated that there is most interest in the collection of tritiated water vapour rather than of tritium gas or the hydrocarbons but the reasons for this are not given in the report.

Reviews of this kind are, of course, intended partly as a source of references to original work and methods, but all too often subjects are discussed in an over-generalized and inconclusive way. This criticism cannot be applied to the present report; the most important methods are described and discussed in detail. Tables are presented describing the various methods for incorporating biological tissues into liquid scintillators and comparing the methods of measurement of tritium in liquids and on surfaces (indicating sensitivities available with each method). Recommendations are made on the best liquid scintillants to be used with aqueous samples and a list is given of world suppliers of tritium standards of various kinds. However, despite the attention given to comparison between methods, a person new to the field might not appreciate from the report the relative practical difficulties in methods involving ionisation chambers and proportional counters as compared with liquid scintillation techniques.

Operational monitoring methods for tritium in air, in liquids and on surfaces are described under the "computer age" heading "Real-time measurement". This section compares the methods using ionization chambers, gas flow proportional counters and scintillation methods for tritium in gaseous streams. This reviewer is left with the impression that he must have been unfortunate on the occasions when he used portable tritium-in-air equipment, as there is no suggestion in the report that such equipment might be unreliable when subjected to the rigours of field measurements.

The report would be an obvious first step for an individual with a particular problem in the measurement of tritium, but is also recommended as a standard reference text for the health physics office or for any laboratory in which tritium is used.

G. S. Linsley.

1977, *British Journal of Radiology*, *50*, 340–349

Radioisotopic study of the adrenal glands using ^{131}I–19-iodocholesterol*

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Abstract

Scintigraphy of the adrenal gland with ^{131}I–19-iodocholesterol has recently been added to radiological techniques in adrenal imaging and has been used successfully to demonstrate anatomical and functional disorders of the adrenals in a variety of clinical situations. A review of the authors' experience stresses the diagnostic value of this method. Radiological findings and results of scintillation imaging are complementary: their comparison improves and clarifies indications for scintigraphy.

Hyperadrenal cortical diseases always gave satisfactory scintigrams, the most interesting results being obtained in adrenal cortical hyperplasia and unilateral hyperfunctioning adenomas. In these cases the evaluation of the response to stimulation or suppression tests was very useful. On the other hand scintigraphy was less valuable in demonstrating malignant and non malignant tumours.

^{131}I–19-iodocholesterol, despite its many limitations, is still the agent of choice in adrenal scintillation scanning (Beierwaltes *et al.*, 1971; 1974; Lieberman *et al.*, 1971; Conn *et al.*, 1972; Anderson and Beierwaltes, 1974; Troncone *et al.*, 1974 a), 1975; Britton *et al.*, 1975; Duffy *et al.*, 1975).

Other products have been proposed in the past as possible adrenal glands tracers, but either the poor radiochemical characteristics or insufficient adrenal uptake have prevented the achievement of satisfactory results (Bengtsson, 1963; Hanngren *et al.*, 1964; Counsell *et al.*, 1968; Di Giulio and Beierwaltes, 1968; Nagai *et al.*, 1968; Nagai, 1970). On the other hand radioactive iodocholesterol appears adequate for imaging the adrenals because it is regularly and consistently concentrated. The suitable physical properties of ^{131}I make it easily detected by both rectilinear photoscanners and Anger cameras (Counsell *et al.*, 1970; Blair *et al.*, 1971).

In a previous paper the methodological and dosimetric aspects of this new technique were discussed (Troncone *et al.*, 1974 b). We now wish to report our further experience concerning a group of subjects with various adrenal pathologies, selected from more than 60 patients studied, in an effort to evaluate the diagnostic capabilities of adrenal scintigraphy.

TABLE I

Adrenal scintigraphy—38 selected cases

Conditions	Number of cases
Hyperadrenocorticism	
Cushing	14
Aldosteronism	8
Virilization	6
Adrenocortical Insufficiency	
Addison	3
Prednisone therapy	1
Malignant Tumours	
Adrenocortical Ca.	1
Sarcoma	1
Pheochromocytoma	3
Chemodectoma	1

Material and Methods

Adrenal gland scintigraphy with ^{131}I–19-iodocholesterol was performed in 38 subjects referred to us suspected of having adrenal disease. The group included patients with established Cushing's syndrome, primary aldosteronism, virilizing syndrome and a number of other benign and malignant adrenal disorders (Table I). In every case the diagnosis was made by the usual clinical tests and radiological examinations. In some cases (nine) there has been surgical confirmation. Eight patients who were scanned did not show any involvement of the adrenal glands, even after a close inspection.

The method of examination is simple and in its general principles follows the original method of Beierwaltes *et al.*, (1971). Daily scans were performed two to ten days after the intravenous injection of 0.7–1.5 mCi of ^{131}I–19-iodocholesterol using potassium perchlorate ($KClO_4$) as a thyroid blocking agent (800 mg daily by mouth in four divided doses) (Barbarino *et al.*, 1975).

Patients were in a prone position when the scans were performed. When the Anger camera was used the patient was positioned in front of the detector with the collimator touching his back and centred on the first or second lumbar spinous process.

After adrenal scanning a renal scan was found to be useful in relating the position of the adrenal tissue to the kidney. Kidney localization was performed after the injection of 200 μCi of ^{197}Hg-Chloromerodrin intravenously with an appropriate setting of the pulse height window. Taking advantage of the different gamma energy of the ^{197}Hg (0.080 MeV) and ^{131}I (0.364 MeV), without moving the patient the pulse height analyzer was reset for ^{131}I and the patient rescanned. In this way it is possible to transfer the outline of the kidney to the adrenal scan and to obtain a scintigraphic representation of both adrenals and the kidney outlines simultaneously. The following landmarks on each side were located on the back of the patient and transferred to the dot paper scan and the photoscan: the 11th and 12th thoracic and the posterior costal margins.

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* Paper presented at the third Congress of the European Association of Radiology. Edinburgh, 22–27 June, 1975.

The adrenal glands were imaged with either a 12.5 cm × 7.5 cm crystal rectilinear photoscanner, provided with a 13 cm focus and 55 hole collimator, or with an Anger gamma-camera (Pho-Gamma HP Nuclear Chicago) with a 1000 hole collimator, coupled to a small computer system with a 64 × 64 dot matrix (Laben).

When the rectilinear scanner was used, the pulse-height window width was 100 KeV centred on the ^{131}I gamma energy (0.364 MeV). The scanning speed was 40–60 cm min^{-1}. The distance of the head from the patient's back was 4–5 cm in subjects with normal weight and muscular development. When the Anger camera was used the pulse-height window was centred on the ^{131}I gamma peak; Polaroid pictures were obtained routinely both from the oscilloscope of the camera and from the cathode-ray tube display of the computer system. Scintiphotos were taken with a count setting of 30 000–60 000 depending upon the available count rates.

An adrenal gland suppression test was performed by giving Dexamethasone, 3 mg orally daily, beginning two days before the ^{131}I-19-iodocholesterol injection and continuing until the adrenal scans were completed. The stimulation test was performed by giving ACTH (Synacthen depot) i.m. two days before iodocholesterol administration.

Results

Normal adrenal scintillation scan and camera picture

Figure 1 shows the normal scintillation scan and camera picture of the adrenal glands. Scan images

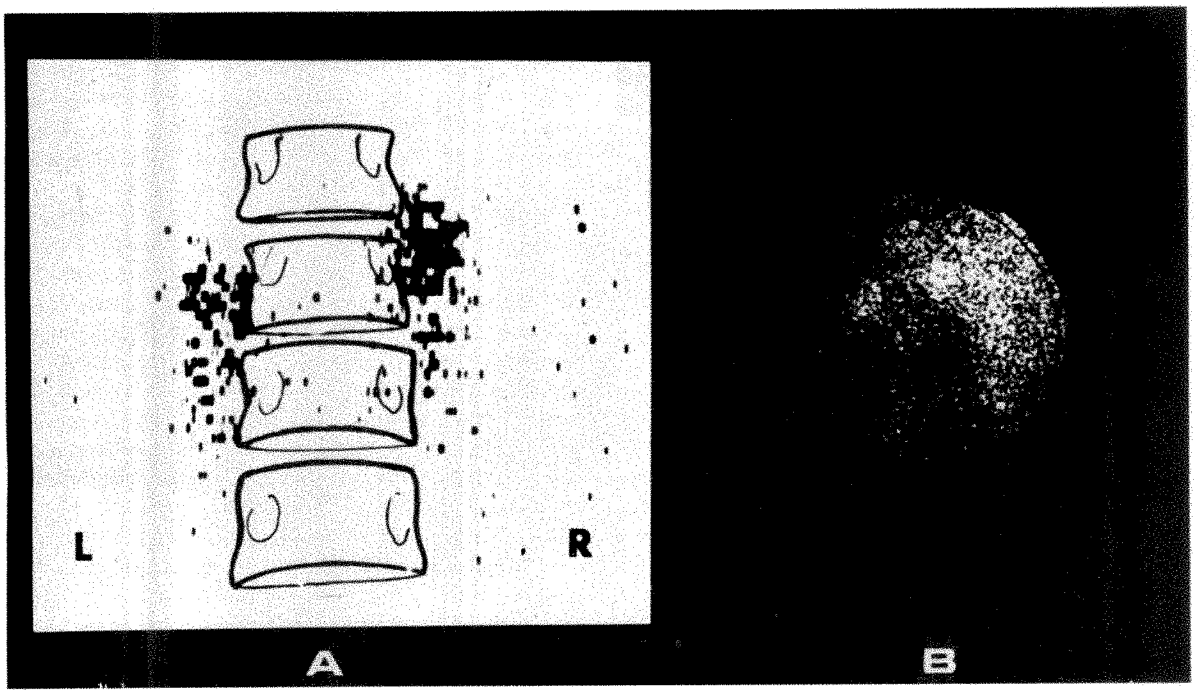


Fig. 1.

Rectilinear photoscan (A) and Anger camera (B) pictures of normal adrenals (posterior view).

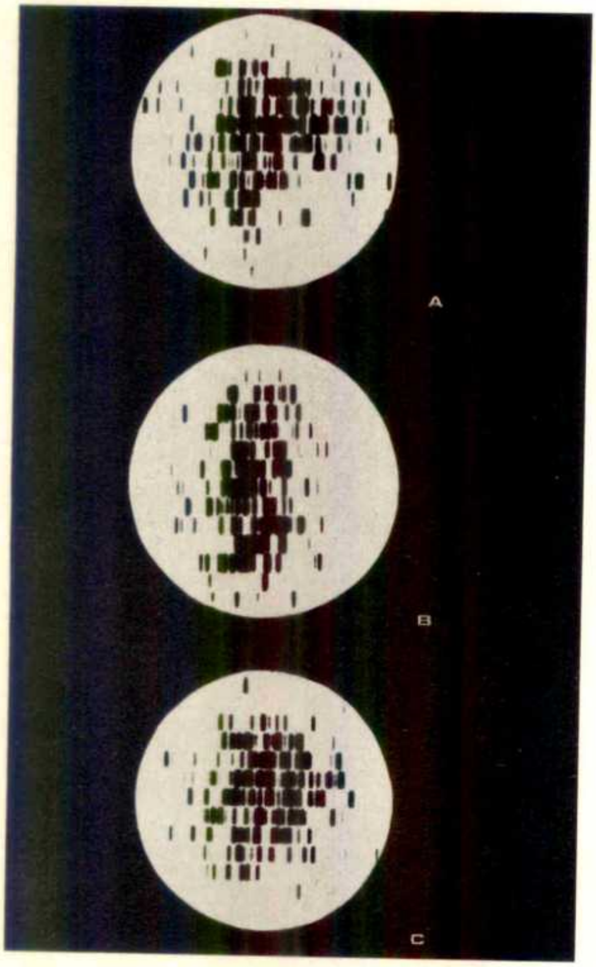


Fig. 2.

The different morphological aspects of the adrenals as seen on scintillation scan (triangular, lengthened, circular).

(Fig. 1a) are clear and characteristic. Normally the right gland seems to be more globose and active than the left one and is usually placed higher.

With camera pictures, there is a rather different image (Fig. 1b): both glands appear as bright areas, circular and similar in shape and activity distribution. The adrenal morphology, therefore, in our experience seems to be better represented by scanning which is able to demonstrate the variation in the outline of the gland: rather triangular or circular on the right side, oval or lengthened on the left side (Fig. 2). In addition, the photoscans are more directly comparable with anatomical and angiographic findings. The adrenals appear in their natural location with respect to the kidney: the right one on top of the upper renal pole, the other on the upper internal margin of the left kidney (Fig. 3). Gas introduced for retroperitoneal pneumography tends to lift both the diaphragm and adrenal glands so that they usually appear placed higher, above the kidneys and triangular in shape.

Abnormal adrenal images

Since hyperadrenocorticism gives the most satisfactory scans, it is in this group of diseases that adrenal scintigraphy seems to find its particular indication. In every case investigated, scintigraphy gave a good adrenal location, while radiological examination was unsuccessful or contraindicated in three patients (because of hypertensive attacks). Adrenal scintigraphy, associated with stimulation or suppression tests, often proved to be conclusive in distinguishing adrenal gland hyperplasia from a unilateral hyperfunctioning adenoma and, consequently, cortisol-producing from aldosterone or androgen-producing adenoma.

Figure 4 shows a case of bilateral adrenocortical hyperplasia well demonstrated by adrenal angiography and equally well by scintigraphy (Fig. 4c). However scintigraphy gives a direct image of the enlargement of the glands which appear more radioactive than those of normal adrenal glands, where there is a rather uniform distribution of radioactivity in glands of approximately equal size. In this case the hyperplasia is evident. If the suppression test with Dexamethasone had been carried out it would have produced a marked decrease of iodocholesterol uptake in both adrenal glands.

There is a very different response in the case of cortical adenomas. Schematically, we have two different kinds of picture. In the aldosterone or androgen secreting adenoma, associated with primary aldosteronism or virilizing syndromes respectively, both adrenal glands are well visualized (an adenoma is sometime scarcely evident as hyperactive area inside the gland). But in this case the Dexamethasone suppression test decreases the iodocholesterol uptake of the normal adrenal tissue outside the adenoma leaving the adenoma uptake unchanged. Thus the adenoma will become more easily recognizable on the scan, correctly indicating the side of the lesion. The camera pictures (Fig. 5) show this kind of hyperfunctioning adenoma in a case associated with a virilizing syndrome. The tumour area, scarcely evident on the right gland under basal conditions (because it does not depress the cholesterol uptake outside the nodule), is quite clearly detected after Dexamethasone administration. The scan can thus give a precise picture of the adrenocortical alteration in function.

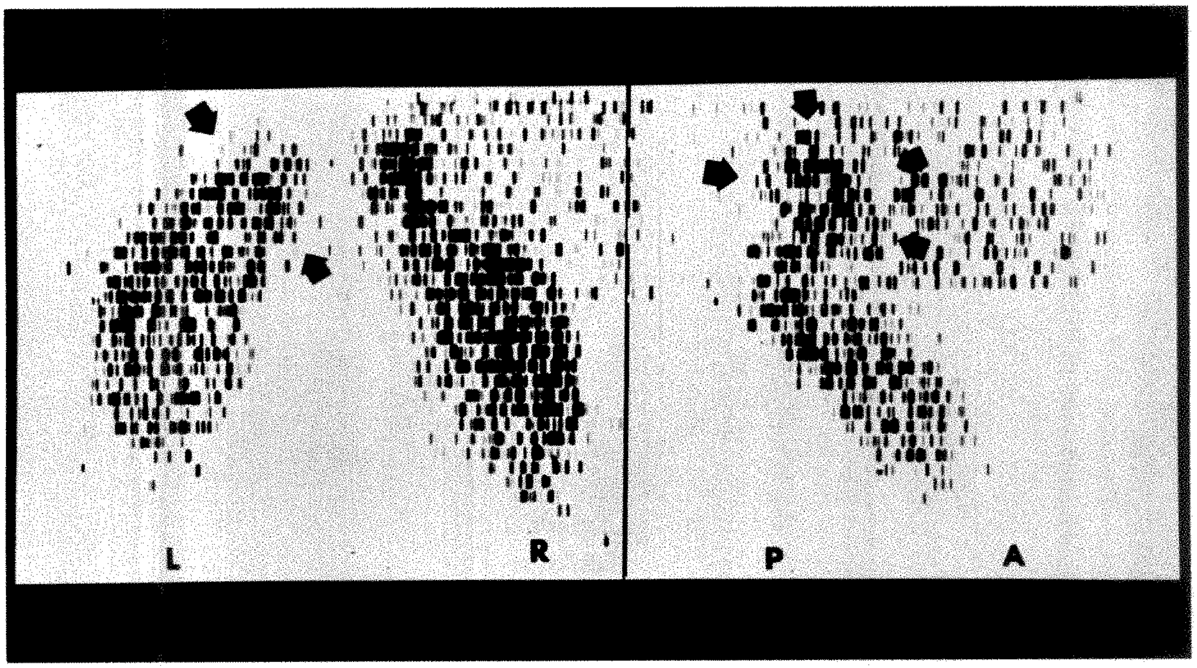


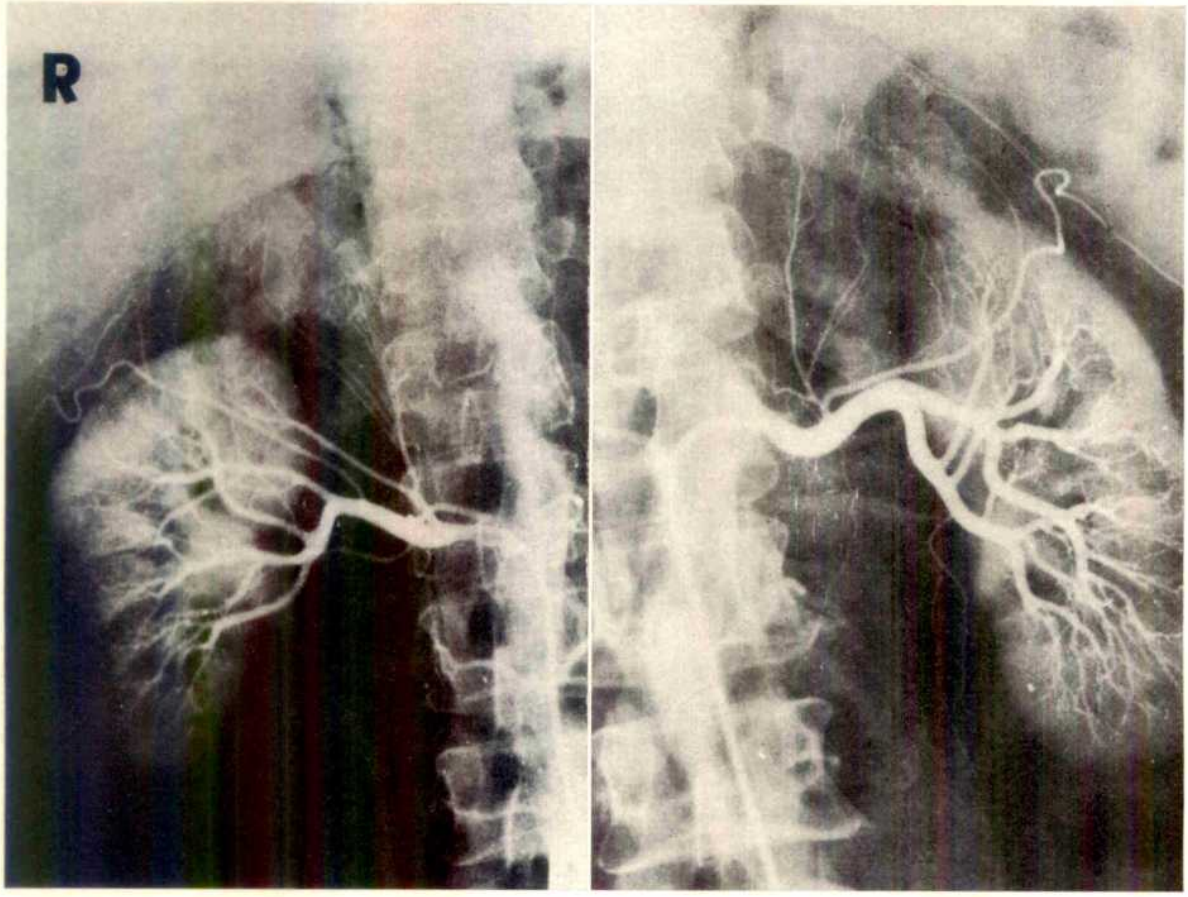
FIG. 3.
Relationship of the adrenal glands to the kidneys studied by simultaneous scintigraphic representation of both adrenal and kidney outlines (posterior and lateral view: 7th day after iodocholesterol administration). The photoscans are comparable with anatomic and angiographic findings.

On the other hand the cortisol-secreting adenoma produces a hormone capable of depressing uptake in the adrenal gland outside the nodule so the preponderant or total uptake of radioactive cholesterol will be only on the side of the tumour. The presumed mechanism is suppression of pituitary ACTH by excess cortisol resulting in sub normal stimulation of normal adrenocortical tissue. In order to confirm the diagnosis, an ACTH stimulation test can be carried out. A scan after ACTH administration shows the resumption of radioactivity in the suppressed adrenal tissue. The patient in Fig. 6 had an adrenocortical tumour in the left gland proved by angiography. Adrenal scintigraphy not only demonstrates the tumour but also displays its level of function. It is typical of an adenoma producing excess cortisol sufficient to raise the serum concentration to levels associated with Cushing's syndrome. An ACTH stimulation test also producing a normal uptake in the opposite adrenal gland confirms the diagnosis.

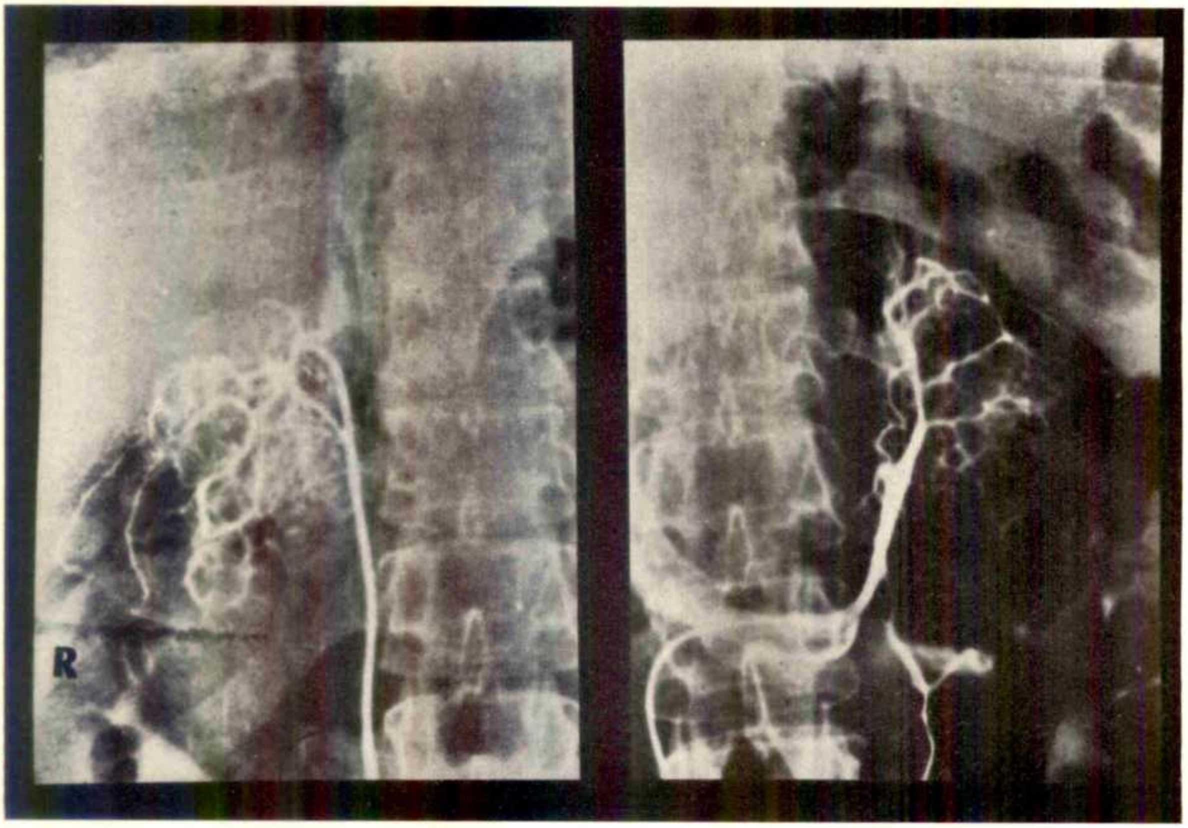
In malignant tumours or medullary tumours which do not take up iodocholesterol scintillation scanning pictures give less specific and less complete results than angiographic ones. An adrenocortical malignant tumour usually appears on the scan as a non radioactive area in the gland with the tumour. Figure 7A shows an adrenocortical carcinoma secreting testosterone with complete destruction of the right gland. In this case adrenal selective arteriography (Fig. 7B) outlines the mass more precisely and visualizes its pathological vessels.

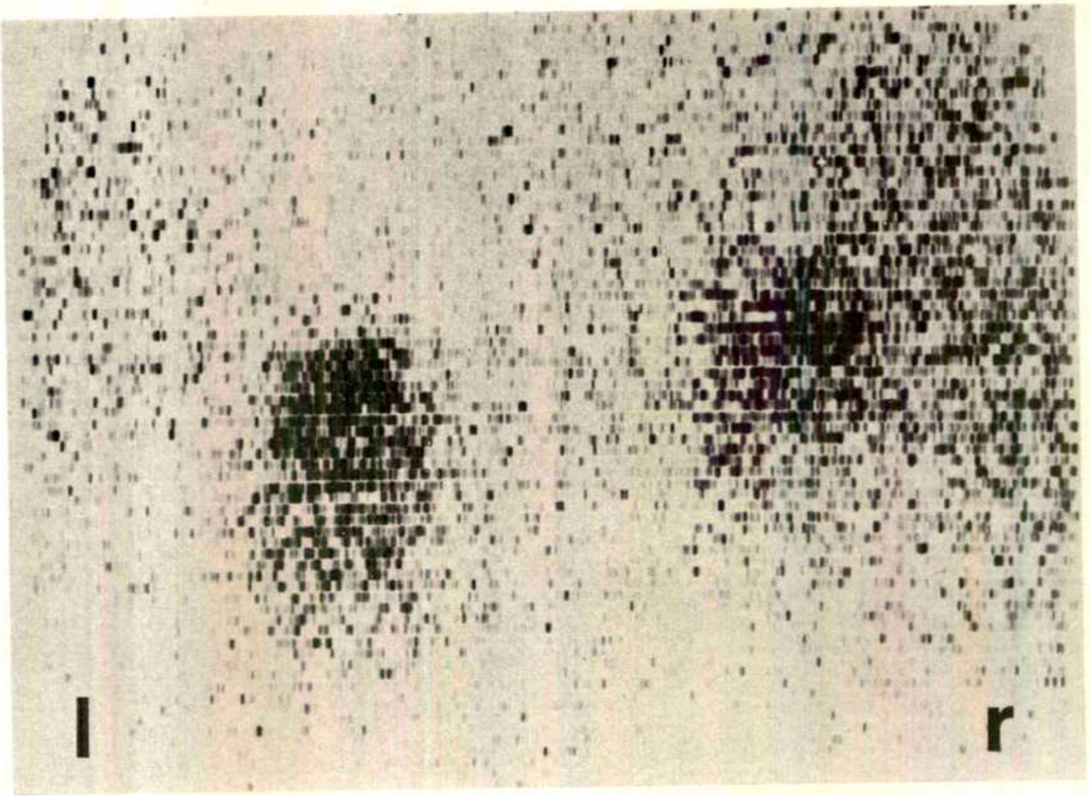
Even large adrenal medullary tumours (Fig. 8) may give similar scans (a chemodectoma in this case), resulting in lack of visualization of the affected gland. But a small and well limited medullary tumour may appear as a cold area or a little notch on the edge of the gland. In the case scanned (a benign pheochromocytoma), a curved notch is clearly visible around the edge of the suprarenal (Fig. 9). These are, however, as already mentioned, not specific images but are by no means unimportant as far as diagnosis is concerned. When the tumour has preserved partial function it may be especially opportune to exclude the existence of an adenoma. In any case a preliminary evaluation is necessary before passing on to a complex and possibly hazardous test such as angiography.

Hypoadrenocorticism does not seem to present any particularly interesting or characteristic image. Generally the adrenal glands fail to visualize, and the high radioactive content of extra-adrenal tissue



A





C

FIG. 4.

Bilateral adrenocortical hyperplasia (Cushing's Syndrome) well demonstrated by (A) Arteriography, (B) Venography and (C) Scintigraphy (6th day). The photoscan gives the direct image of the adrenal enlargement.

makes the glands difficult to recognize. In these cases adrenal scintigraphy may be useful to evaluate the loss or occasional resumption of adrenocortical function (*e.g.* after surgical resection, after adrenocortical steroid medication, after venography when extravasation of contrast material may have occurred, etc.)

DISCUSSION

Our data, even though still limited, confirm the validity of adrenal scintigraphy. Possibly the ^{131}I–19-iodocholesterol does not constitute an ideal compound for visualizing the adrenal glands: the radioactivity injected is rather higher than is usually used for diagnostic purposes so that the absorbed radiation doses are not negligible (Kirschner *et al.*, 1975). Iodine-131, although quite good for scintillation scanners, is less favourable for the Anger camera because of its high energy gamma rays. However, at present, it is the only agent available which concentrates selectively in the adrenal glands. The mechanism of concentration is probably due to the

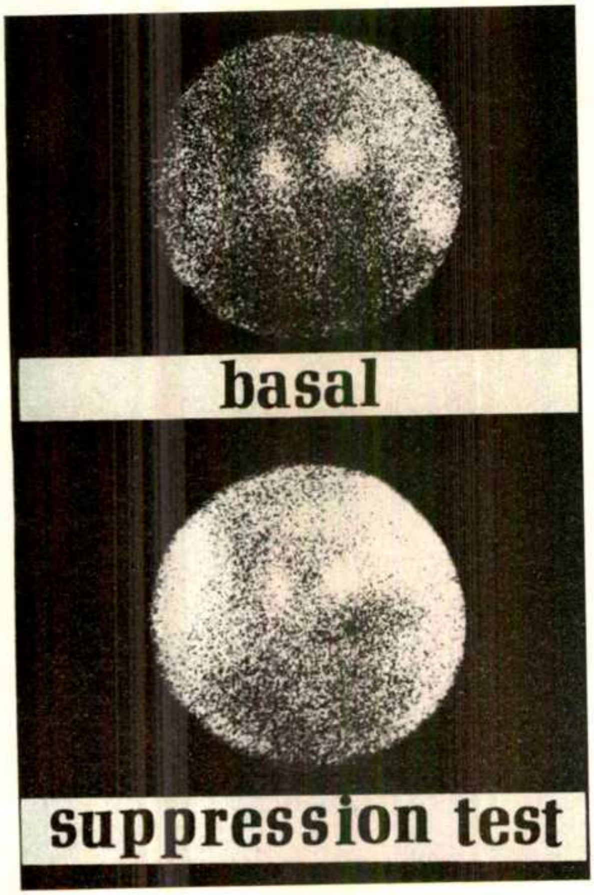


FIG. 5.

Hyperfunctioning adenoma associated with a virilizing syndrome. Anger camera picture (5th day) before (top) and after (bottom) Dexamethasone administration. See text for description.

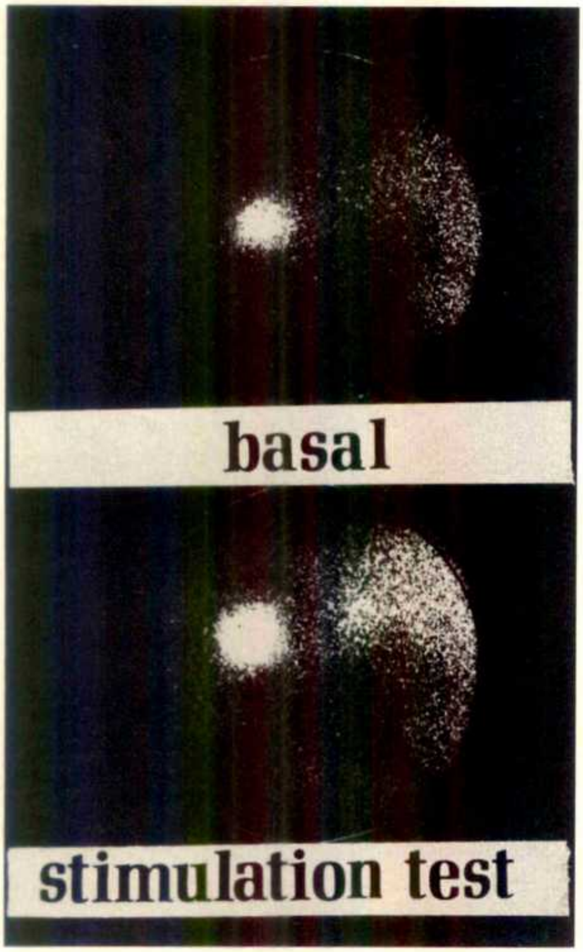
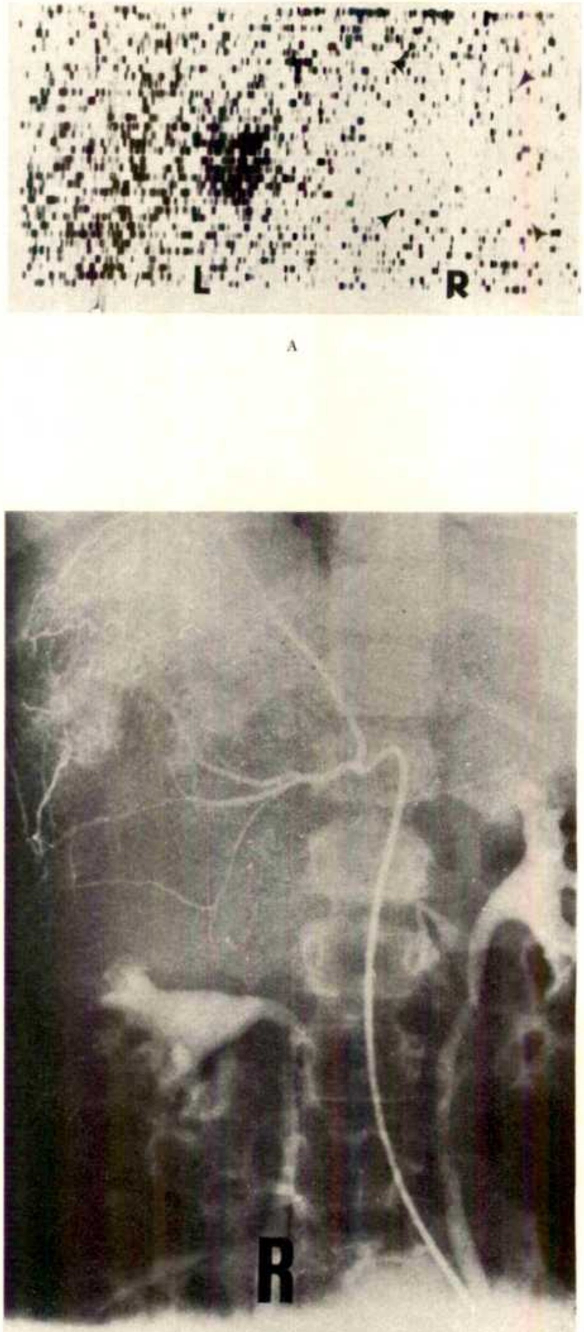


FIG. 6.

Cortisol secreting adenoma. Anger camera scan (3rd day) before (top) and after (bottom) ACTH administration. The adenoma produces an excess of cortisol capable of depressing the iodocholesterol uptake in the adrenal tissue outside the nodule.

fact that cholesterol represent the principal precursor of adrenocortical steroids (Beierwaltes *et al.*, 1971; Samuels and Uchihawa, 1967). In the extra-adrenal tissues the radioactivity, although rather elevated at first, rapidly diminishes, resulting—within four to six days—in high target to non target ratios (Beierwaltes *et al.*, 1971; Troncone *et al.*, 1974b). So a good representation of the adrenals, in their natural situation, is possible. Consequently, a study can be made of their morphology and function, and any alteration whether global or limited can be detected.

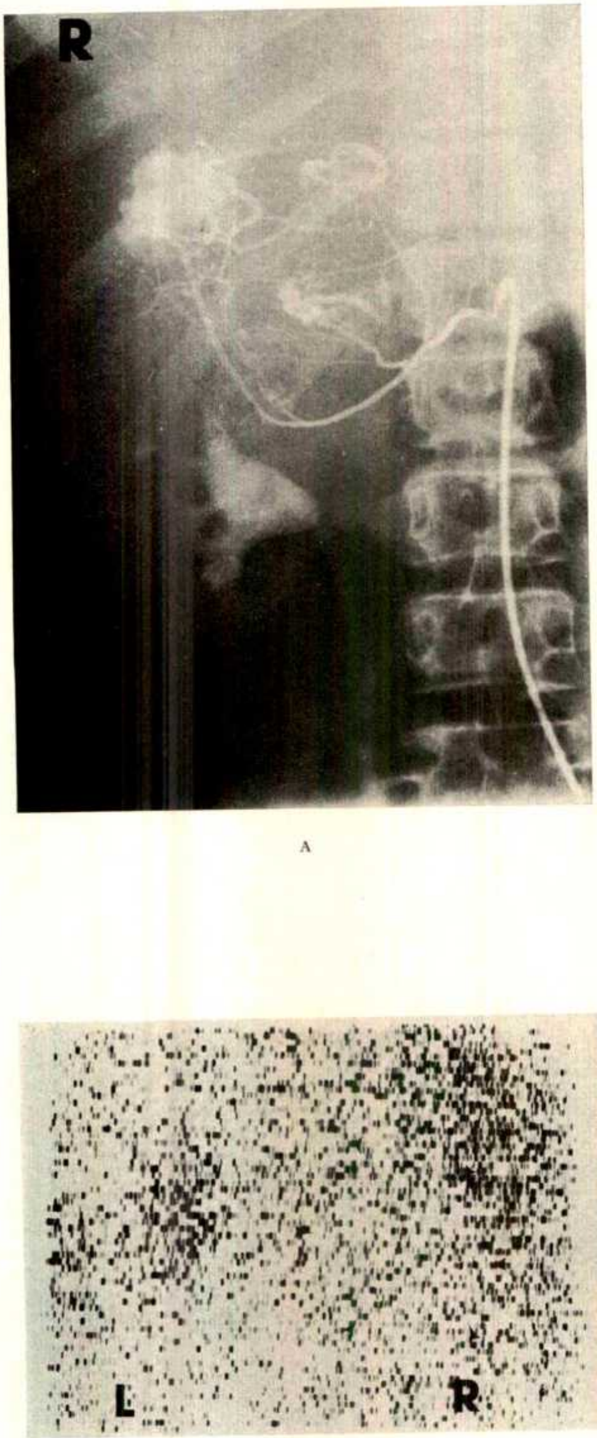


A

B

FIG. 7.

Adrenocortical carcinoma associated with a Virilizing syndrome. (A) The tumour appears on the photoscan (7th day) by a lack of visualization of the tumour-bearing gland. (B) Selective arteriography outlines more precisely the mass and visualizes its pathological vessels and pooling of the contrast medium.



A

B

FIG. 8.

Even large adrenal medullary tumours may result in a photo-scan with lack of visualization of the affected gland. (A) Selective arteriography. (B) Adrenal scintigraphy (7th day). See text for description.

With its simplicity and lack of hazard it should be included (of course in well selected patients) as a useful and often indispensable complement to radiological examination. In some cases, and in particular in the case of functioning tumours, adrenal gland scintigraphy may also be an alternative method of investigation. In fact, especially if associated with stimulation or suppression tests, adrenal scintigraphy by itself can be conclusive in revealing hyperfunctioning adenomas and, among these, in distinguishing the cortisol-producing from aldosterone or androgen-producing adenomas.

A number of prospective applications have been suggested including the treatment of hyperfunctioning tumours and functional investigation of adrenocortical glands (Anderson and Beierwaltes, 1974; Morita *et al.*, 1972). The first point does not seem at present feasible owing to the small adrenal-concentration of the labelled iodocholesterol. However, the second one, really does seem to open new possibilities for research into the field of adrenal pathology where so much still has to be explored.

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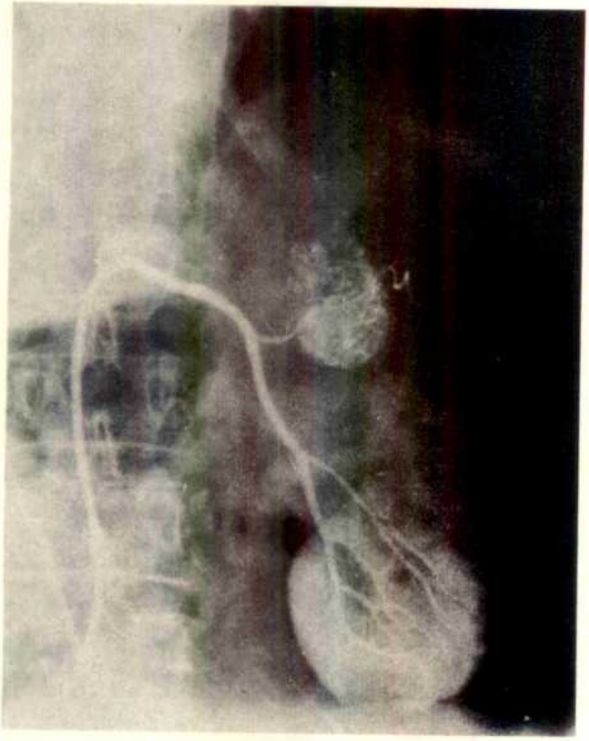
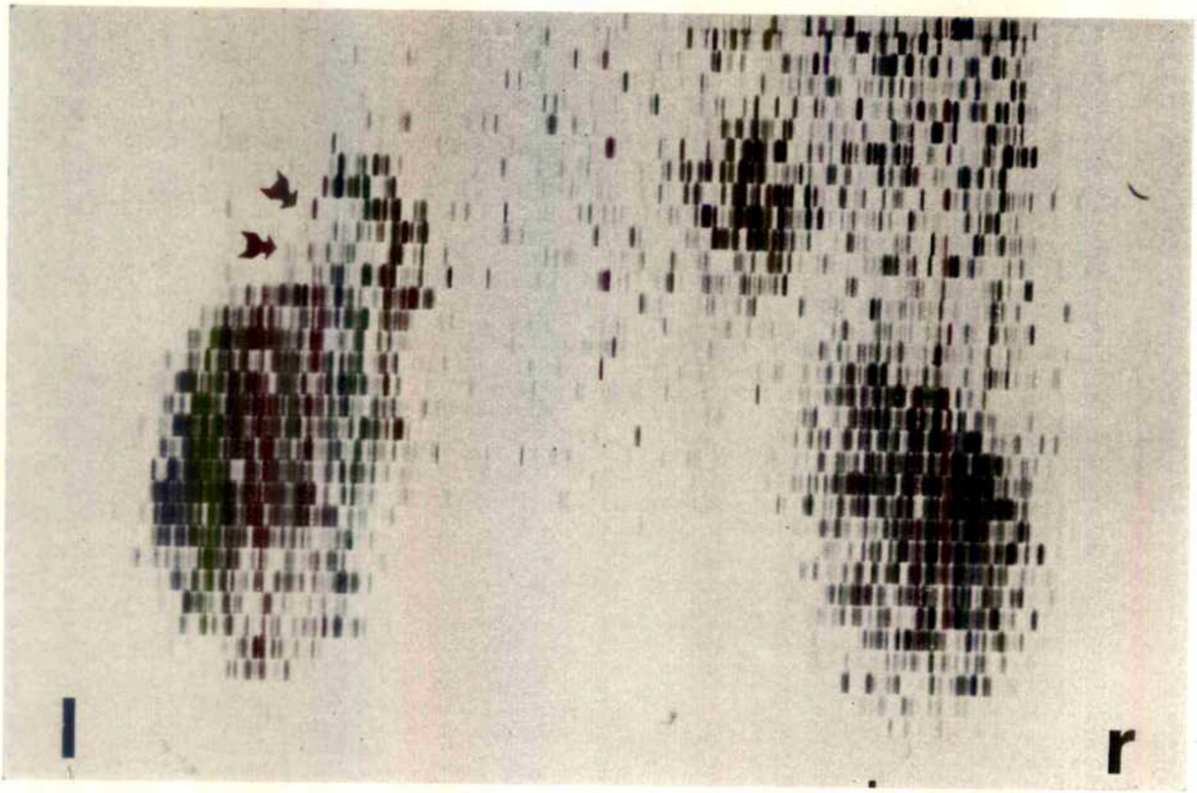


A

FIG. 9.

Benign pheochromocytoma. (A) Selective arteriography. (B) Adrenal scintigraphy: on the photoscan (8th day) the small tumour appears as a curved notch around the edge of the left gland.



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Book reviews

Directory of on-going research in cancer epidemiology. Pp. 461, 1976. I.A.R.C. (France), $5.00 (to cover postage and packing).

This directory is a joint effort of the International Agency for Research in Cancer (IARC), Lyon, France and the German Cancer Research Centre (DKFZ), Heidelberg, within the framework of the International Cancer Data Bank Programme of the National Cancer Institute (NCI) of the U.S.A.

It contains data from some 40 countries concerning current epidemiological studies on human cancer. The information is produced as a short summary in each case, giving the names of workers and the place of research. In many instances, considerable detail is given about studies and in others just an indication of the research being undertaken. There can be no doubt about the value of a directory such as this for establishing links between interested parties. It also helps to avoid much reduplication of research. For any such publication to be useful, it must be well indexed and the system used is excellent. It includes lists of the principal investigators, collaborators, tumour sites, aetiological factors, types of studies undertaken, population based cancer registries, etc.

Brendan Hale.

International Directory of Specialized Cancer Research and Treatment Establishments. pp. ix + 521, 1976. First Ed. UICC Technical Report 23. Published under the auspices of the Committee on International Collaborative Activities by the Union Internationale Contre le Cancer, $30.00.

This directory gives details of various institutes throughout the world, such as the main cancer-related personnel and activities undertaken in the establishments. There are details of numbers of staff employed, their annual cancer-patient statistics where appropriate and often budgetary matters. In addition there is an indication of training facilities and also the availability of libraries and their size. The existence of any cancer registry facilities at the centres is also noted.

Brendan Hale.

1977, *British Journal of Radiology*, 50, 350–356

Photon absorptiometry of bone after successful renal transplantation

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(*Received June, 1976 and in revised form February, 1977*)

Abstract

Photon absorptiometric measurements of the right lower femur were carried out at regular intervals of one to three months in 58 recipients of renal transplant.

(1) During the first six months after transplant, 57% showed a significant and abnormal rate of loss of bone mineral (mean 11.7% per year. ±1.1% S.E.M.) while 30 months' after transplantation only 17% showed such a significant loss ($p = 0.025$).

(2) Eighteen months after transplantation both male and female recipients of transplants had a significantly lower mean bone mineral index than controls ($p < 0.001$).

(3) Male patients who developed new post-transplant fractures had a lower mean bone mineral content compared with age and sex-matched controls taken from transplant recipients without such fractures ($p < 0.01$). Similarly male patients with post-transplant fractures had a significantly longer mean period on regular haemodialysis ($p < 0.05$) compared with patients without such fractures.

Regular photon absorptiometric measurements provide an accurate, informative and non-invasive technique for following changes of bone mineral content after successful renal transplantation.

Disturbances of calcium metabolism and ensuing osseous complications remain an important cause of morbidity in uraemic patients successfully treated by renal transplantation (Pierides *et al.*, 1974a; Moorhead *et al.*, 1974; Pierides *et al.*, 1975). Secondary hyperparathyroidism and osteomalacia present during regular haemodialysis gradually resolve (Pierides *et al.*, 1974b) but osteoporosis develops (Carroll *et al.*, 1973; Huffer *et al.*, 1975). This progressive osteoporosis has been related to the development of post-transplant fractures (Griffiths *et al.*, 1974) and also the development of avascular necrosis of bone (Lindsay *et al.*, 1975). Thus accurate measurements of changes in bone mineral are of paramount importance. In this respect, routine radiological skeletal surveys may not be ideal as they are not sufficiently sensitive to detect small changes in bone mineral content. Similarly, the usefulness of serial transiliac bone biopsies may be limited by their invasive nature and known site to site variation of total bone in the ilium (Ellis and Peart, 1972).

Photon absorptiometry allows comfortable and accurate assessment of bone mineral changes. Banzer and Schneider (1973), Atkinson *et al.* (1973) and Griffiths *et al.* (1973) have reported on the use of this method in uraemic patients during regular haemodialysis and after renal transplantation. Lindsay *et al.* (1975) have described loss of bone mineral in 90% of their patients during the first post-transplant year.

We present here the results of serial measurements of bone mineral content in renal transplant recipients in Newcastle upon Tyne.

Material and Method

Since May 1974 all new successfully transplanted uraemic patients have had serial bone scans at intervals of one to two months. Patients transplanted before May 1974 were also scanned at about the same time and then followed at intervals of two to three months. Fifty-eight patients, 32 male and 26 female, with five or more serial measurements are included in this report. The average number of measurements was eight per patient. Their mean age was 40 (22–58).

All the patients were looked after by the Department of Medicine, University of Newcastle upon Tyne. They received azathioprine at a dose of about 3 mg/kg/day and prednisone starting at 40 mg daily and reducing to 10 mg daily by the end of the first year. Acute rejection episodes were controlled with intravenous methylprednisolone.

The findings in these patients were compared with those of 17 male and 14 female non-uraemic controls with a mean age of 38 (22–56).

A method similar to that of West and Reed (1970) was used to scan the lower end of the right femur. Two parallel scans, 1 cm apart were taken at each visit. For each patient the upper scan was always taken at a constant measured distance from the upper border of the patella.

The radiation source was the characteristic radiation from a samarium target excited by the primary X-ray beam from a superficial therapy X-ray tube operated at 100 kV, 10 mA. Measurements of attenuation coefficients in various pure elements indicate that the beam is virtually monochromatic with a quantum energy of 42 keV. The detector used was a scintillation counter. The pulses from this were analysed and fed into a multiscaler where the completed scan was stored until punched on to paper tape for computer processing.

At each visit a measurement of bone mineral in mass per unit length was obtained and this was called the Bone Index. Serial measurements from each patient were fitted by a straight line using the method of least squares in order to calculate the rate of change and allow comparison between patients. The resulting rate of change was tested for its difference from zero slope.

Errors and reproducibility

Bone index, as measured by the single energy, constant thickness technique is subject to certain systematic errors. These are related to (a) problems of scanning with a finite beam (Watt, 1973) and (b) the effects of adipose tissue (Dalen and Jacobson, 1974). The former are of no consequence when serial measurements are taken provided the collimation and speed of scanning remain constant. The effect of adipose tissue becomes important if there is a change in the fat content during the follow-up period, since an increase in fat content could be interpreted as a loss of bone mineral. Compensation for this error was achieved by measuring the attenuation coefficient of the soft tissue adjacent to bone at each patient's visit and using it in the calculation of the patient's bone index. This essentially abolished any error due to changes in soft tissue composition or vascular calcification associated with corticosteroid therapy, assuming these changes to be homogeneously distributed around the bone.

The random errors of the technique are associated mainly with counting statistics and patient repositioning. The inherent reproducibility of the technique expressed as the standard deviation of a set of phantom measurements was 1.5%. A similar value can be obtained *in vivo* if several scans are made without repositioning. However, serial measurement on individuals are subject to a larger error due to the difficulty of repositioning accurately. The

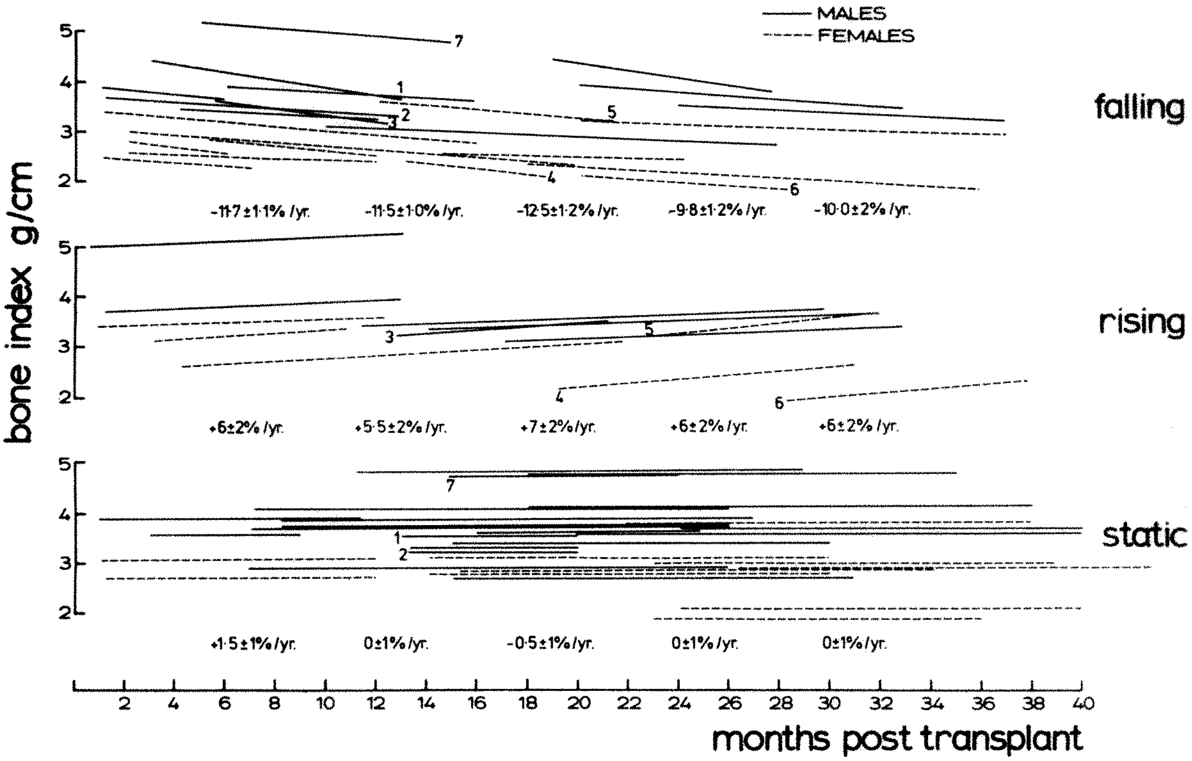

FIG. 1.

Serial measurements in 58 patients fitted by straight lines. The %/yr values are mean values of slope (±standard error of mean) for each group of patients at 6 monthly intervals.

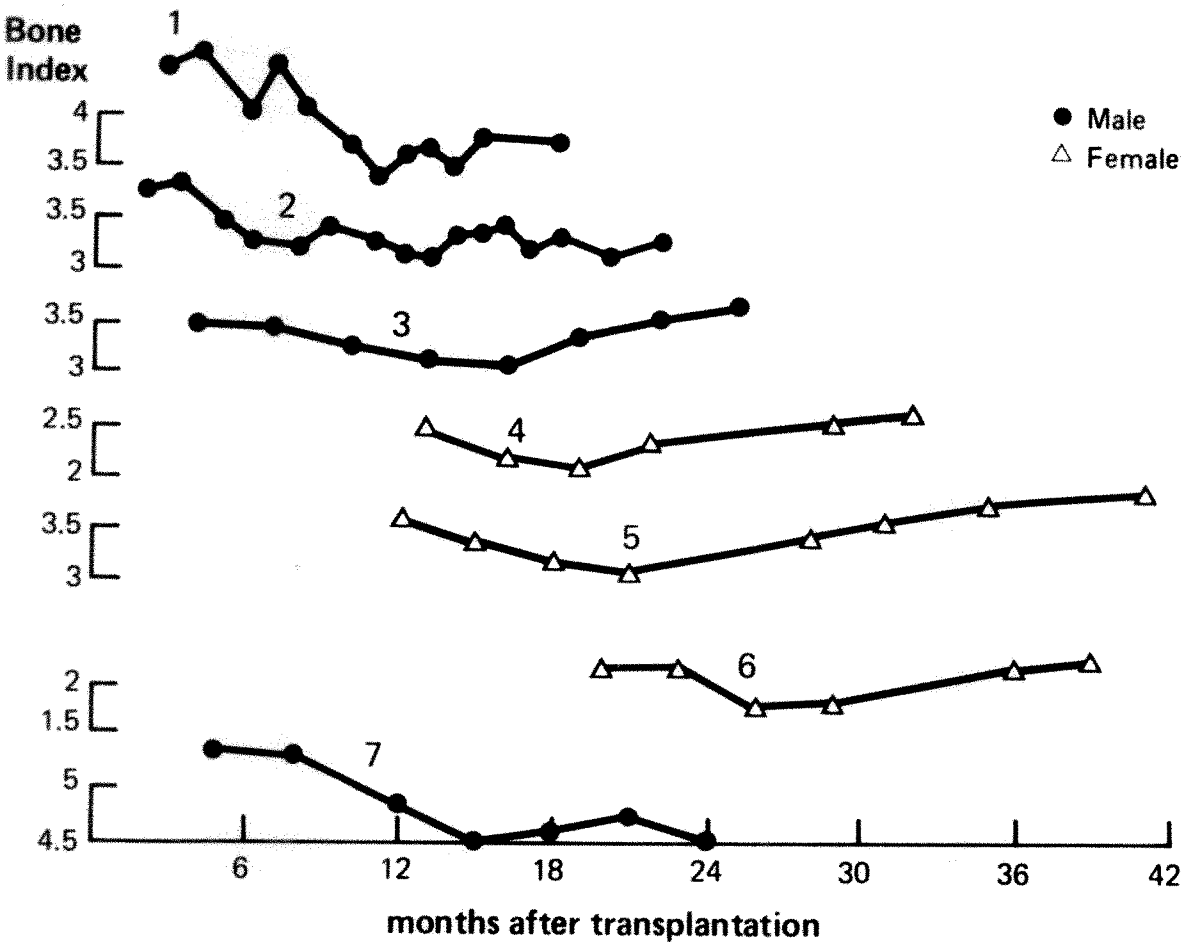

Fig. 2.

Actual measurements in seven patients showing a change in slope.

overall precision of *in vivo* measurements of bone mineral was determined by replicate measurements on 19 normal subjects. The two measurements were separated by intervals varying from three to eight months. The standard deviation of these measurements was 3.4%. A slightly higher value (4.5%) was found for patients. This was determined by calulating a variance for the measurement on each patient where bone mineral could be assumed to be changing linearly with time and finding the average value for all these patients.

Results

Figure 1 illustrates the results from serial measurements in the 58 patients studied. Fifty-one are represented by single lines while the remaining seven, who showed a change of slope, are represented by two lines (numbered one to seven). The actual measurements of these seven patients are shown in

TABLE I

Number of patients remaining static, losing or gaining, 6, 12, 18, 24 and 30 months after transplantation

Time since transplant (months)	Total no. of patients (overall rate of change per year)	No. of patients falling (%)	No. of patients rising (%)	No. of patients static (%)
6	21 (−5.4±1.9%)	12 (57%)	5 (24%)	4 (19%)
12	25 (−5.1±2.0%)	12 (48%)	5 (20%)	8 (32%)
18	28 (−3.0±1.6%)	6 (21%)	5 (18%)	17 (61%)
24	34 (−1.6±1.0%)	8 (23%)	5 (15%)	21 (62%)
30	24 (−0.9±1.0%)	4 (17%)	6 (24%)	14 (59%)

Fig. 2. All seven patients initially showed a significant loss of bone mineral. In all of them this loss gradually ceased and in four it was followed by a gain. The change of slope was significant by the variance ratio method in two of them. Table I summarizes the data by considering the number of patients remaining static, losing or gaining at six-monthly intervals after transplantation. As time since transplantation increased there was a progressive reduction in the number of patients losing bone mineral, so that by 30 months post-transplant the number of patients losing bone mineral was significantly lower compared with the number of patients losing bone mineral during the first six months ($p = 0.025$, Table II). For the 21 patients with serial measurements within the first six months, no relationship could be demonstrated between the rate of loss of bone mineral and the age, sex, diagnosis, duration on regular haemodialysis, length of hospital stay during the transplant operation or total prednisone therapy during the first three months (Table III).

TABLE II

STATISTICAL ANALYSIS SHOWING A SIGNIFICANT REDUCTION IN THE NUMBER OF PATIENTS LOSING BONE MINERAL 30 MONTHS AFTER TRANSPLANTATION

	No. of patients at		
	6 months	30 months	
Falling	12	4	16
Static and rising	9	20	29
	21	24	45

Chi-squared = 5.019 $p = 0.025$.

Amongst the 58 patients studied, there were 19 who developed new skeletal fractures during the first two years after transplant. These fractures were detected by serial skeletal radiographs. All 19 patients had a transiliac bone biopsy one year after transplantation which showed no osteomalacia. Table IV compares the mean bone mineral index in these patients with fractures with that of age and sex-matched controls taken from transplant patients without fractures. Male patients with fractures showed a significantly lower mean bone mineral index ($p < 0.01$) than their controls. In females no significant difference could be found between the

TABLE III

CLINICAL DETAILS ON 21 PATIENTS WITH SERIAL BONE MINERAL MEASUREMENTS DURING THE FIRST SIX MONTHS

Name	Sex	Age	Diagnosis	Duration on haemodialysis (months)	Length of hospital stay (days)	Prednisone therapy* methyl prednisolone, g, in first three months	Rate of change of Bone Index (% per year)
Losing							
J.K.	M	46	Gout	5	27	6 (2 courses)	−12
T.S.	M	37	Chronic pyelonephritis	36	16	3 (1 course)	−16
L.W.	M	50	Malignant hypertension	7	18	3 (3 courses)	−14
K.L.	M	47	Glomerulonephritis	32	56	9 (3 courses)	−12
M.H.	M	39	Malignant hypertension	60	46	9 (3 courses)	− 6
A.R.	F	46	Med. cystic disease	1	33	12 (4 courses)	−15
L.C.	F	22	Malignant hypertension	25	15	NIL	− 8
C.G.	F	56	Glomerulonephritis	27	14	3 (1 course)	−15
J.M.	F	49	Analgesic nephropathy	1	12	6 (2 courses)	−14
J.R.	F	58	Glomerulonephritis	2	15	6 (2 courses)	−10
F.S.	F	50	Polycystic disease	40	30	9 (3 courses)	− 5
B.S.	M	33	Gout	0	11	6 (2 courses)	−10
Gaining							
T.Mc.	M	46	Haemolytic/uraemic syndrome	11	22	6 (2 courses)	+ 5
J.W.	M	52	Chronic pyelonephritis	32	18	3 (1 course)	+ 5
J.C.	F	47	Cystinuria	28	15	6 (2 courses)	+ 5
J.I.	F	39	Polycystic disease	10	30	9 (3 courses)	+10
J.P.	F	23	Chronic pyelonephritis	15	47	12 (4 courses)	+ 7
Static							
A.M.	M	53	Chronic pyelonephritis	39	30	6 (2 courses)	+ 3 N.S.
J.W.	M	60	Malignant hypertension	11	67	9 (3 courses)	0
J.N.	F	31	Chronic pyelonephritis	12	21	6 (2 courses)	+ 3 N.S.
D.C.	F	61	Chronic pyelonephritis	9	15	6 (2 courses)	0

* Basic prednisone treatment was the same in all patients: 40 mg/day for two months, 35 mg/day for third month.

mean bone mineral indices. The mean period on regular haemodialysis was longer for males with fractures than for those without fractures ($p < 0.05$, Table V). In females there was no significant difference between the mean periods on haemodialysis.

Table VI compares the mean bone index in normal subjects and transplant recipients. Measurements made 18 months after transplantation were used for this comparison. Both male and female patients had significantly lower bone indices than non-uraemic controls ($p < 0.001$). In both groups males had higher bone indices than females ($p < 0.001$).

DISCUSSION

Changes in bone mineral content

A decrease in the mineral content of the os calcis was demonstrated by Banzer and Schneider (1973) in six out of seven transplanted uraemic patients and similar loss of mineral content was observed by Lindsay *et al.* (1975) in 90% of their patients during the first post-transplant year. Atkinson *et al.* (1973) confirmed a similar loss of bone in two of their patients. Our findings are in agreement with the above observations but also indicate that, at least in the lower end of the femur, this loss occurs mostly during the first year after transplant and the incidence thereafter gradually declines. A minority of patients (Fig. 1) showed a gain, in keeping with the findings by Griffiths *et al.* (1973) who, after studying 123 transplant recipients, concluded that after transplantation a few patients showed a gain, while the majority showed a significant loss. Our data suggest that statements about changes of bone mineral must be qualified by information about the interval after transplantation at which the measurements are made. Most patients could be expected to show a loss of bone mineral in the first post-transplant year but it may be of more prognostic significance if this loss continues for two or three years.

TABLE IV

COMPARISON OF MEAN BONE INDICES IN MALE AND FEMALE PATIENTS WITH AND WITHOUT NEW POST-TRANSPLANT SKELETAL FRACTURES

Transplant patients with fractures	Transplant patients without fractures Matched for age and sex	
Bone Index		
Male 3.40 ± 0.15 g.cm^{-1} ($n = 8$)	4.14 ± 0.17 g.cm^{-1} ($n = 8$)	$t = 3.26$ $p < 0.01$
Female 2.63 ± 0.15 g.cm^{-1} ($n = 11$)	2.98 ± 0.16 g.cm^{-1} ($n = 11$)	$t = 0.51$ N.S.

Severe losses of bone mineral content after transplantation had been reported earlier by radiological techniques. Hampers *et al.* (1969) noted demineralization of the spine in 33% of their transplant patients while Popovtzer *et al.* (1972) observed varying degrees of radiographic skeletal rarefaction. Griffiths *et al.* (1974) found an increased concavity of vertebral bodies and diminution of the number of trabeculae in the long bones, both signs of progressive osteopenia. Histologically, Carroll *et al* (1973) noted changes of bone mineral loss in some of their iliac crest bone biopsies and Huffer *et al.* (1975) observed, in sections of trabecular vertebral bone obtained at autopsy, a decrease in bone volume. Forty-one per cent of 17 long-term transplant patients showed a reduced bone volume and none showed an increase.

Mechanisms of bone mineral changes

Successful renal transplantation is followed by a number of endocrine changes that can affect bone mineral balance. There is restoration of normal $1{,}25(OH)_2D_3$ metabolism and in pre-menopausal women there is a return of menstruation and improved ovarian function. Indeed three of the four patients (Fig. 2) whose bone loss reversed to a gain

TABLE V

COMPARISON OF MEAN PERIODS ON REGULAR HAEMODIALYSIS

Transplant patients with fractures	Transplant patients without fractures	Difference between means	t*	p
Male: Mean: 32 ± 5 S.E.M. Range: 10–55 months	Mean: 15 ± 4 S.E.M. Range: 0–32 months	17 ± 6.4	2.66	< 0.05
Female: Mean: 31 ± 5 S.E.M. Range: 3–84 months	Mean: 28 ± 5 S.E.M. Range: 2–73 months	3 ± 7.1	0.43	N.S.

* The t test assumes that the times are normally distributed which is difficult to prove in this case. A non-parametric test was also used, which gave the same result for p in both cases.

TABLE VI

COMPARISON OF BONE INDICES BETWEEN NORMAL SUBJECTS AND PATIENTS 18 MONTHS AFTER TRANSPLANTATION

Control	Patients 18 months after transplantation
Male 4.26 ± 0.06 g.cm^{-1} $n = 17$	3.69 ± 0.06 g.cm^{-1} $t = 6.7$ $n = 18$ $p < 0.001$
Female 3.52 ± 0.08 g.cm^{-1} $n = 14$	2.80 ± 0.05 g.cm^{-1} $t = 7.6$ $n = 11$ $p < 0.001$
$t = 7.4$ $p < 0.001$	$t = 11.1$ $p < 0.001$

The uncertainties are standard errors of the mean.

were young women in whom menstruation returned after renal transplantation. As opposing factors one needs to consider the amount of corticosteroid therapy given to these patients and the occasional persistence of secondary hyperparathyroidism. The importance of secondary hyperparathyroidism and excessive bone resorption mediated by parathyroid hormone was exemplified by three patients with particularly severe osteitis fibrosa at the time of transplantation (histological grades 3.5, 4.0 and 4.5, Ellis and Peart, 1973). All showed a steady loss of bone mineral after the transplant. One of these three patients was treated with long-term intramuscular salmon-calcitonin and the progressive mineral loss was reversed (Case 3, Fig. 2). In four patients previously treated by parathyroidectomy, photon absorptiometric measurements remained impressively static throughout their follow-up, suggesting a possible role for parathyroid hormone in post-transplant osteoporosis.

Most likely the most important factor contributing to post-transplant osteoporosis is corticosteroid therapy. Although Table III suggests that there is no apparent linear relationship between steroid dosage and changes in bone mineral, this does not mean that steroids are of no significance. The amount of prednisone received by these patients during the first three months is clearly supraphysiological and a maximal loss of bone mineral could occur at doses below those received by the patients.

Clinical significance of bone mineral loss

Avascular necrosis of bone and fractures are the main skeletal problems encountered in transplant patients and both have been linked to progressive osteoporosis (Griffiths *et al.*, 1973; Lindsay *et al.*, 1975). Lindsay *et al.* (1975) found that transplant patients who subsequently developed bone necrosis had significantly lower bone mineral content immediately after grafting than their counterparts, but the mean loss thereafter was not significantly different. We have not made early post-transplant measurements of bone mineral in all our patients who later developed bone necrosis, but in a previous study in our centre (Pierides *et al.*, 1975) there was no correlation between the development of avascular necrosis and bone status as defined by histology and radiology at the time of renal transplantation. Furthermore, female patients who have low bone indices did not show an increased incidence of bone necrosis.

Osteopenia and accelerated loss of bone mineral may be aetiologically important in the development of new post-transplant fractures as seen in 19 of our 58 patients. These 19 patients had a lower mean bone index than age and sex-matched patients without fractures; the difference was particularly significant in males, suggesting that osteoporosis could have contributed to the development of the fractures. It is of interest that new fractures develop mostly during the first 12 months after transplantation when the rate of bone mineral loss is maximal. This would suggest that both a high rate of bone mineral loss and a low absolute bone mineral value are important contributing factors. This considerable loss of bone mineral after renal transplantation may be of particular significance in the patients who lose their grafts and return to regular haemodialysis, since occasionally such patients later develop non-osteomalacic fractures which could be related to the patients' immobilization and exposure to large amounts of corticosteroids.

Photon absorptiometry after transplantation appears important and worthwhile. Our experience since May 1974 suggests that it could be used routinely in the follow-up of transplant patients and that in conjunction with radiology it can help to identify patients at risk of developing severe osteoporosis and fractures. Quantitative bone histomorphometry on transiliac bone biopsies could be reserved for patients where specific information about osteomalacia and osteitis fibrosa is required.

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Book review

Nuclear Medicine and Ultrasound. Edited by Leonard M. Freeman and M. Donald Blaufox, pp. 169, 1976 (New York, Grune and Stratton, Inc), £8·25.

This volume is a reprint of articles which appeared originally in Seminars in Nuclear Medicine (one chapter from January 1974, the remainder in the October 1975 issue). It represents the integrated concept in diagnostic imaging, the emphasis being on the relative value of the two techniques from a clinical standpoint. The material is well covered, with particularly useful chapters on cardiovascular disease, and on the liver and pancreas. Inevitably the rapid technical developments occurring in both subjects mean that some of the material is out of date. For example, there are relatively few grey scale ultrasonograms. (Perhaps this accounts for the surprising statement that isotopes are as useful as ultrasound in placental localization.) Newer pharmaceuticals for imaging the biliary tract are not mentioned nor are tumour-seeking agents, and dynamic brain scanning is only briefly referred to. Similarly in the renal section, whereas the place of ultrasound in characterizing urographic mass lesions is properly emphasized, the claimed usefulness of isotope images is questionable. Surely the isotope techniques are most valuable in providing functional information so that it is sad that the renogram is not mentioned at all.

Notwithstanding points of this sort, this collection is a useful survey of the two fields, and one looks forward to similarly directed studies of the relative usefulness of whole body computer tomography, isotope and ultrasonic scans.

D. E. Cosgrove.

1977, *British Journal of Radiology*, *50*, 357–359

Technical notes

The use of screened low energy radiation sources for moulds

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It is well-known that large squamous carcinomas in the mouth have a low cure rate with conventional radiation treatment. Attempts may be made to improve this situation by implantation of sources or treatment with an intra-oral cone, but as these may be difficult to control applicators are often preferred.

The conventional oral radium applicator is uncomfortable for the patient to wear and is associated with considerable exposure to staff. In addition, the high energy γ rays are difficult to screen and radiation tolerance under these circumstances may be reached, not by the tumour and its immediate structures, but by normal tissues in the neighbourhood. Maximum screening of associated normal tissues can be achieved by using ^{125}Iodine, a radioisotope which emits X and γ rays of 27–35 keV. This is available in seeds which are useful for the manufacture of small or large applicators (Sealy *et al.*, 1976) and which are acceptable to patients because of their light and elegant form.

EXAMPLE OF IODINE-125 MOULD

The following is an illustrative case report.

A patient, aged 56, presented with a ten-month history of an enlarging ulcer on the roof of the mouth. Examination showed a mainly papillary carcinoma, 5 cm in its greatest diameter, at the junction of the hard and soft palates. The tumour extended to the apex of the tonsillar fossa and down the anterior pillar of the fauces, almost to the lateral margin of the tongue. No nodes were palpable in the neck. Histology confirmed the diagnosis of a squamous carcinoma. Other investigations were non-contributory.

A course of cobalt therapy was given through two opposing 10 × 8 cm fields to a mid-plane exposure of 2000 R in five fractions in four days overall time. Six weeks after completing this treatment, there was total regression of the papillary element of the tumour, and of the tumour extending into the apex of the tonsillar fossa and down the anterior pillar of the fauces. An ulcerating tumour, however, remained at the junction of the hard and soft palates. It was accordingly decided to treat this with a ^{125}I mould as shown in Fig. 1. The mould which was worn as a denture plate was made by taking a Zelgan impression using a conventional upper dental tray with a "Stent" extension taking in as much of the soft palate as possible.

A 2 mm acrylic base plate was constructed on this model and the ^{125}I seeds mounted on it. The seeds were fixed in position with "sticky wax" and covered with 2 mm of "Ash" soft metal (Gauge 7), which contains 97% tin (Fig. 2), to protect the tongue and floor of mouth. The plaque was secured with cold cure acrylic around the periphery. A "Stent" bite block, together with the patient's lower denture and an under-jaw bandage, helped keep the base plate *in situ*. The 43 sources, of activities ranging from

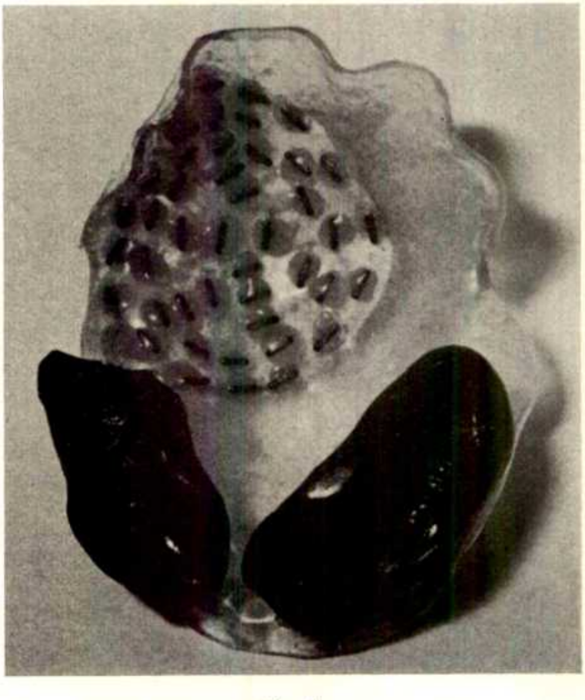

FIG. 1.

Iodine mould showing the mounted seeds.

0.68 to 3.45 mCi, were distributed over the area (15.75 cm^2) of the plate. The thickness of the plate ranged from 1 to 2 mm.

For the dose calculations the sources were considered to be lying in a single plane as shown diagrammatically in Fig. 3. The sources near the pointed end of the area were chosen to be of a slightly higher activity than those on the opposite part of the plane and in this way a fairly uniform dose distribution was achieved across the area (as shown in Fig. 3).

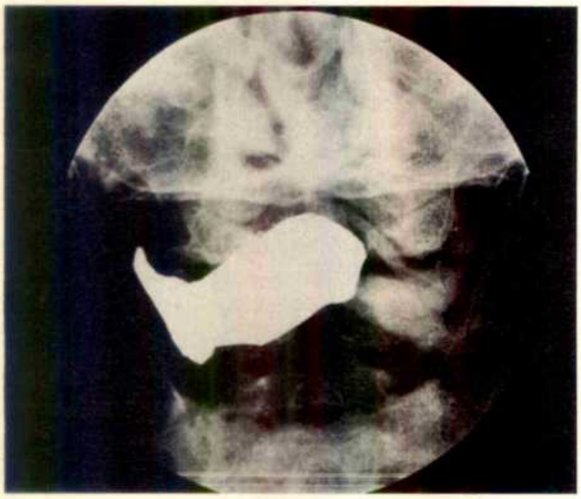

FIG. 2.
X-ray (A.P.) showing the position of the metal shield in the patient's mouth.

The dose rate at 0.5 cm from the plane of the sources was found to be 47 rad/hr. The patient wore the mould eight hours a day for seven consecutive days, thus receiving a total dose of 2630 rad at a distance of 0.5 cm from the plane of the sources.

For the dose calculations a half-value thickness in tissue of 2 cm and an "absorbed dose factor" of 1.7 rad/hr^{-1} mCi^{-1} at 1 cm were used as recommended by Hilaris and Holt (1971). Experiments are under way to obtain more exact dose rates since it seems that the quality of the radiation changes considerably with distance from the source. The ^{125}I dose distribution compares reasonably well with distributions obtained using ^{226}Ra needles, ^{192}Ir wire or ^{192}Ir wire cut into 0.45 cm segments, the latter being positioned in the same way as the iodine sources (Fig. 3) The number and position of the ^{226}Ra needles and the length and position of the

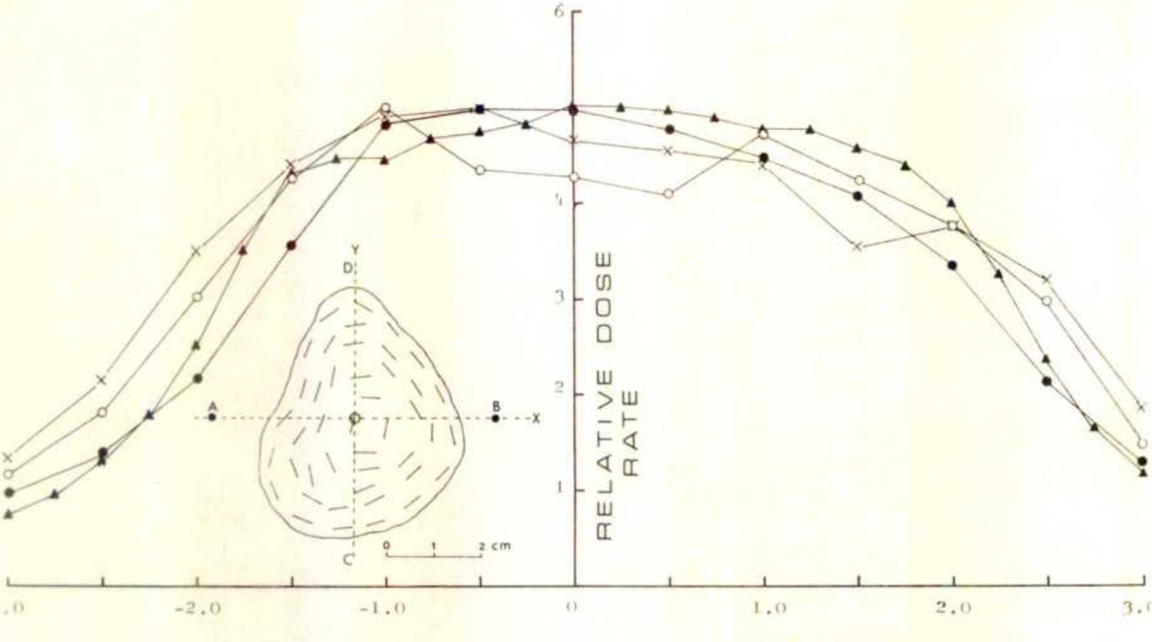

FIG. 3.
Comparison of the variation in dose rate along AB, 0.5 cm from the plane of ^{125}I, ^{226}Ra and ^{192}Ir sources respectively.

—▲—▲— 43 ^{125}I sources

—○—○— 15 ^{226}Ra tube sources in two rings and central spot

—●—●— ^{192}Ir sources in same positions as iodine sources

—×—×— ^{192}Ir wire in two rings and central spot.

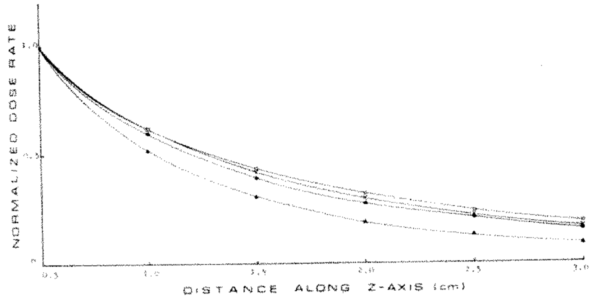

FIG. 4.

Variation in dose rate (normalized to the value at 0.5 cm) along a line perpendicular to the plane of sources and passing through ○ indicated in Fig. 3.

—▲—▲— ^{125}I sources
—○—○— ^{226}Ra sources
—●—●— ^{192}Ir sources in the same position as the iodine sources
—×—×— ^{192}Ir wire.

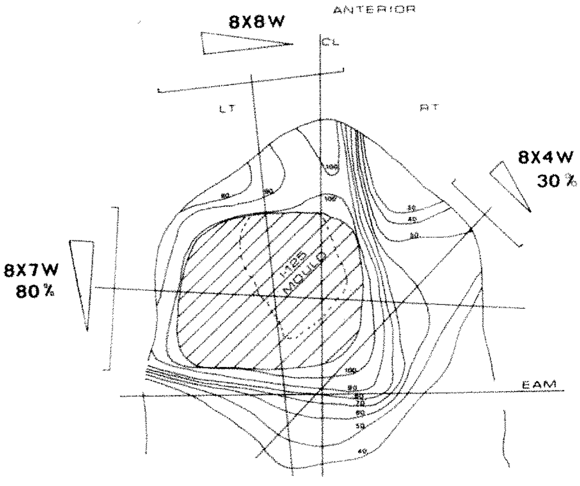

FIG. 5.

A two-dimensional isodose distribution resulting from the cobalt-60 fields is shown. The dotted line indicates the position of the mould.

^{192}Ir wire was determined according to the rules laid down by Paterson and Parker (1938). In Fig. 4, the "% depth dose" is compared for the various types of source. The results are normalized to the dose at a point 0.5 cm from the plane of the sources. All doses were calculated at points on a line perpendicular to the source plane and passing through (Z-axis).

Following this treatment, a confluent membranous reaction ensued which settled within a period of 12 days. Thereafter, the patient received a further course of planned cobalt therapy to a tumour dose of 3000 rad in 15 fractions in 21 days. The distribution and the relationship to the applicator is shown in Fig. 5.

DISCUSSION

This case illustrates well the ease with which an increased dose can be given to a defined portion of the tumour using a screened applicator with no additional radiation to those portions of the tumour requiring a lesser dose or to normal neighbouring tissues. The patient tolerated remarkably easily the wearing of the applicator. Moreover, the radiation reaction from the applicator was limited to the tumour itself.

Two patients have now been treated in this way. One of them (described above) has developed disease in the tongue, whereas the other is well to date.

For radiation protection purposes the exposure rates were measured with the Pitman X-ray Dosimeter Model 37C using a 350 cc chamber which exhibits a flat response at very low X-ray energies (in the region of 30 keV). The maximum exposure rate at the head of the patient was found to be 210 mR/hr and a maximum of 2.7 mR/hr was measured at a distance of two feet from the head. The exposure rate would be of the order of 160 mR/hr at two feet in all directions from the head if ^{226}Ra or ^{192}Ir were used to give the same tumour dose in the same time. This means that for patients treated with ^{125}I in this way personnel exposure is considerably reduced and the patient does not need to be isolated during treatment.

ACKNOWLEDGMENT

Thanks are due to Dr. R. Nurock, Medical Superintendent of the Groote Schuur Hospital, for permission to publish.

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An empirical table of equivalent squares of rectangular fields for the Theratron 780

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Percentage depth-dose tables are generally not available for non-square fields. To accommodate rectangular beams, tables of so called equivalent squares are utilized. Such a table is included in THE BRITISH JOURNAL OF RADIOLOGY, Supplement 11 (and its predecessor, Supplement 10) for use in cobalt teletherapy. The table in Supplement 11 was generated using the mathematical methods of Clarkson (1941) and Meredith and Neary (1944). It was experimentally tested by Kemp and Burns (1958) on the then new Picker C3000 cobalt unit at the London Hospital and has served well ever since.

The Atomic Energy of Canada Ltd., (AECL) Theratron 780 is a typical cobalt irradiator as it has evolved over the past ten years. Sources are now, of course, of much higher activity, collimators and trimmers have been redesigned somewhat, and larger field sizes (up to 35×35 cm at 80 cm SSD) are obtainable. For these reasons and since a new T-780 is in use at this hospital, it seemed desirable to retest the table and, in particular, add the larger field sizes.

Measurements were made using a Capintec 0·6 cm^3 ionization chamber (Farmer type) and electrometer in a large 50×50 cm water phantom. The chamber was waterproofed by inserting it into a Lucite (Perspex) thimble through the side of the phantom. The beam was directed vertically downward so that no material, save water, covered the chamber/thimble combination. The thimble was uniformly 1·5 mm thick. All data were collected with the chamber at 5 cm depth and SSD of 80 cm. Field sizes were adjusted using the scales supplied on the T-780 collimator head. The scales were calibrated using the light field, and coincidence between the light field and the photon field was measured using films and found to agree within 1 mm for the 6×6 cm field and to within 2 mm for the 20×20 cm field.

Since it would have been prohibitive to measure every rectangle in the table, 85 rectangles were chosen whose 5 cm depth-doses differed by no more than 2% and in most cases less than 1%. The true square data points were plotted using ionization readings as ordinate and equivalent areas as abscissa. To these points a smooth curve was fitted. The readings from each rectangle were then used to enter this curve and read the equivalent area.

The data were then plotted into a family of curves with one axis held constant and the other plotted against equivalent area. These were used to fill in the missing rectangles. Since the smallest field size available at the time the measurements were made was slightly larger than 5×5 cm, these data covered the range of 6×6 to 34×34 cm. The 4× and 5× columns were derived by symmetrically sketching their curves into the family. The final table of equivalent squares was made by simply taking the square roots of the equivalent areas and is presented in Table I.

Table II compares selected fields from the table in THE BRITISH JOURNAL OF RADIOLOGY, Supplement 11, with those derived here. The third column is the difference in central-axis depth-dose at 5 cm depth based on the two equivalent squares. It is apparent that no clinically significant difference exists between the two tables although the measured values appear to be consistently larger.

TABLE II

COMPARISON OF MEASURED DATA AND VALUES FROM BRITISH JOURNAL OF RADIOLOGY SUPPLEMENT 11

Field size (cm)	Equiv. square (measured)	Equiv. square BJR–11	Difference in 5 cm % depth dose
6×15	8·9	8·5	+0·5
8×15	10·7	10·3	+0·5
10×15	12·1	11·9	+0·2
12×18	14·6	14·3	+0·3
6×20	9·5	9·0	+0·5
6×30	10·3	9·4	+1·0
10×30	15·0	13·9	+0·9
18×24	20·7	20·3	+0·2
22×28	24·9	24·4	+0·2
22×30	25·3	24·9	+0·1

TABLE I

Equivalent squares of rectangular fields

Cobalt 60

Long axis (cm)	Short axis (cm)																														
	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
4	4·0																														
5	4·4	5·0																													
6	4·7	5·5	6·0																												
7	4·9	5·9	6·6	7·0																											
8	5·2	6·2	7·0	7·5	8·0																										
9	5·4	6·6	7·3	8·0	8·6	9·0																									
10	5·6	6·8	7·7	8·4	9·0	9·5	10·0																								
11	5·7	7·0	8·0	8·7	9·4	10·0	10·5	11·0																							
12	5·8	7·1	8·2	9·0	9·7	10·4	11·0	11·6	12·0																						
13	6·0	7·3	8·5	9·2	10·0	10·8	11·4	12·0	12·4	13·0																					
14	6·1	7·5	8·7	9·5	10·4	11·1	11·8	12·4	13·0	13·5	14·0																				
15	6·2	7·6	8·9	9·8	10·7	11·3	12·1	12·8	13·4	13·9	14·5	15·0																			
16	6·3	7·7	9·0	10·0	10·9	11·7	12·4	13·1	13·9	14·4	14·9	15·5	16·0																		
17	6·4	7·9	9·1	10·2	11·2	11·9	12·7	13·4	14·3	14·8	15·3	16·0	16·5	17·0																	
18	6·6	7·9	9·3	10·4	11·4	12·1	13·0	13·7	14·6	15·2	15·7	16·5	17·0	17·6	18·0																
19	6·6	8·1	9·4	10·6	11·6	12·4	13·2	13·9	14·9	15·5	16·1	16·9	17·5	18·0	18·5	19·0															
20	6·7	8·2	9·5	10·8	11·7	12·6	13·4	14·1	15·2	15·8	16·4	17·3	17·9	18·5	19·1	19·6	20·0														
21	6·7	8·2	9·6	10·9	11·9	12·8	13·7	14·4	15·4	16·1	16·7	17·7	18·4	18·9	19·5	20·0	20·5	21·0													
22	6·8	8·3	9·7	11·1	12·0	12·9	13·9	14·6	15·6	16·3	17·0	18·1	18·7	19·3	19·9	20·5	21·0	21·5	22·0												
23	6·9	8·4	9·8	11·2	12·2	13·1	14·1	14·8	15·8	16·6	17·3	18·4	19·1	19·7	20·3	21·0	21·6	22·1	22·8	23·0											
24	6·9	8·5	9·8	11·3	12·3	13·2	14·2	15·0	15·9	16·8	17·5	18·7	19·4	20·1	20·7	21·4	22·1	22·7	23·3	23·8	24·0										
25	7·0	8·5	9·9	11·4	12·4	13·3	14·4	15·1	16·1	16·9	17·8	18·9	19·7	20·4	21·0	21·8	22·4	23·1	23·8	24·3	24·9	25·0									
26	7·1	8·6	10·0	11·4	12·5	13·4	14·6	15·3	16·2	17·2	18·0	19·2	19·9	20·7	21·3	22·1	22·8	23·4	24·2	24·7	25·3	25·9	26·0								
27	7·1	8·7	10·0	11·5	12·6	13·5	14·7	15·4	16·3	17·3	18·2	19·3	20·1	20·9	21·6	22·4	23·1	23·8	24·6	25·1	25·7	26·3	26·9	27·0							
28	7·1	8·7	10·1	11·6	12·7	13·6	14·8	15·6	16·5	17·4	18·4	19·5	20·4	21·1	21·8	22·6	23·3	24·0	24·9	25·3	25·9	26·5	27·1	27·7	28·0						
29	7·2	8·8	10·2	11·6	12·7	13·7	14·9	15·6	16·5	17·5	18·5	19·6	20·5	21·3	22·0	22·8	23·5	24·2	25·1	25·5	26·1	26·7	27·3	27·9	28·8	29·0					
30	7·2	8·8	10·3	11·7	12·8	13·8	15·0	15·7	16·6	17·6	18·6	19·7	20·7	21·4	22·3	22·9	23·6	24·4	25·3	25·7	26·4	27·0	27·6	28·2	29·3	29·4	30·0				
31	7·3	8·9	10·3	11·7	12·8	13·8	15·1	15·8	16·7	17·7	18·8	19·8	20·8	21·6	22·5	23·1	23·9	24·6	25·5	26·0	26·7	27·3	28·0	28·6	29·7	29·7	30·3	31·0			
32	7·3	8·9	10·4	11·8	12·9	13·9	15·2	15·9	16·8	17·8	18·9	19·9	20·9	21·7	22·7	23·3	24·1	24·9	25·6	26·3	27·0	27·7	28·3	28·9	30·2	30·2	30·8	31·3	32·0		
33	7·3	9·0	10·5	11·8	13·0	14·0	15·3	16·0	16·9	17·9	19·0	20·0	20·9	21·8	22·8	23·5	24·3	25·1	25·7	26·6	27·3	28·0	28·7	29·4	30·5	30·6	31·2	31·8	32·4	33·0	
34	7·4	9·1	10·5	11·9	13·0	14·0	15·3	16·1	17·0	17·9	19·0	20·1	21·0	21·9	22·9	23·7	24·6	25·4	25·8	26·9	27·7	28·4	29·1	29·8	30·7	31·1	31·7	32·4	32·9	33·5	34·0

All dimensions are in cm

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Further simplification of the iridium-192 wire afterloading method using nylon tube

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In an earlier technical note (Payne, 1974), some of the problems associated with the implantation of iridium-192 wire were pointed out and a technique was described which minimized them.

The basic implantation technique is as described by Pierquin (1964), Pierquin *et al.* (1971) and Paine (1972); a 1.2 mm bore nylon tube is threaded through the area under treatment to provide a pathway for a radioactive iridium-192 wire. The wire, which is itself inside a fine nylon tube for strength, and the outer tubing are fixed in the patient by crushing a lead or steel washer onto them.

One of the suggested improvements to this method made by Payne (1974) involved the use of a block and pin system. The nylon tube is prevented from slipping through the wound by a block and pin which does not crush the tube, so that a clear path is left through it. This means that different arrangements of dummy wires or segmented scales can be inserted in the tubes while check films are taken; they can be removed again afterwards without disturbing the implant which is then ready to receive the radioactive iridium-192 wire. Once this has been loaded, it is held in place by crimping a single lead washer onto the nylon tube distant from the active region of the implant. Such an arrangement allows the washer to be manipulated without causing discomfort to the patient. It also simplifies removal of the radioactive wire after treatment; the simplified removal technique was described earlier (Payne, 1974).

The block and pin fixing method proved satisfactory in use for over a year but had the disadvantage that the blocks and pins could not be considered as disposable items, because of the time taken to machine them. A simpler system of restraint has now been devised.

With the co-operation of the Malaysian Rubber Producer's Research Association, a natural rubber latex prevulcanized with radiation* was loaded with 83 g barium sulphate per 100 g dry rubber and was cast into sheets 3.5 mm to 4.5 mm thick. The semi-dried sheets were thoroughly leached in water and re-dried. The choice of polymer and other ingredients as well as the leaching process were determined by a need to minimize the possibility of tissue reaction. Washers were stamped from the sheet, each being a nominal 7.9 mm outside diameter with a central hole punched using a 1.0 mm diameter punch. These washers were loaded in convenient numbers on a mandrel of 22 S.W.G. hardened steel wire approximately 12 cm long; Fig. 1 shows a batch of washers ready for use.†

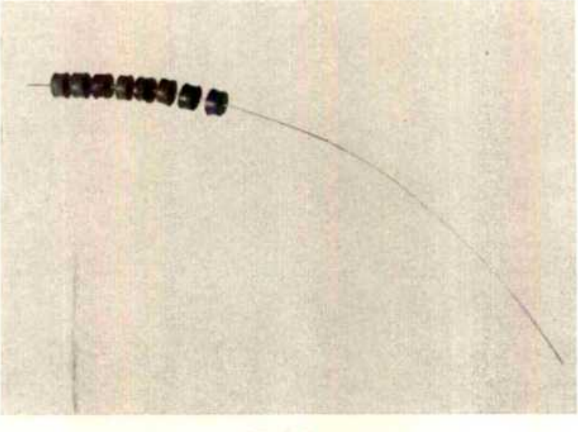

Fig. 1.

Radio-opaque rubber washers loaded on a wire mandrel ready for use.

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* Radiation prevulcanized natural rubber is available as "PRECURTEX" from MAPA, 17–25 Rue de Bagnolet, 93260 Les Lilas, France.

† Washers made from a similar radio-opaque material are now available commercially. Details can be obtained from Aldington Laboratories Ltd., Ashford, Kent.

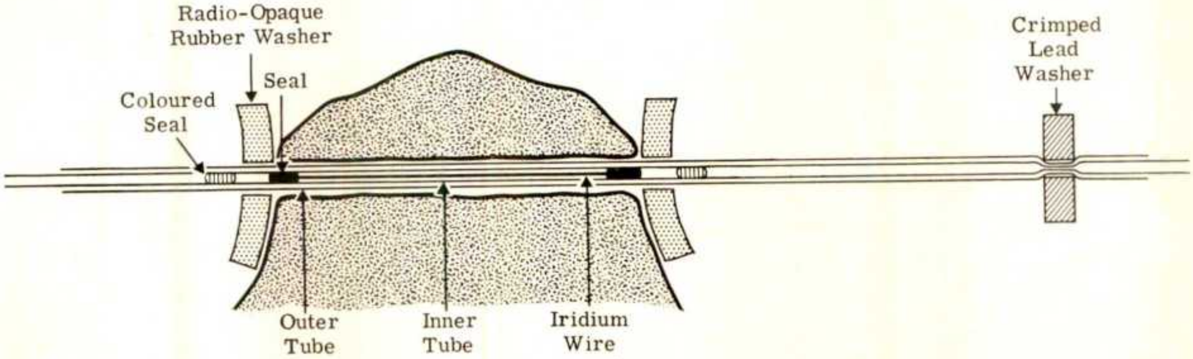

FIG. 2.

A method for securing an iridium-192 wire source using a radio-opaque rubber washer with a crimped lead washer.

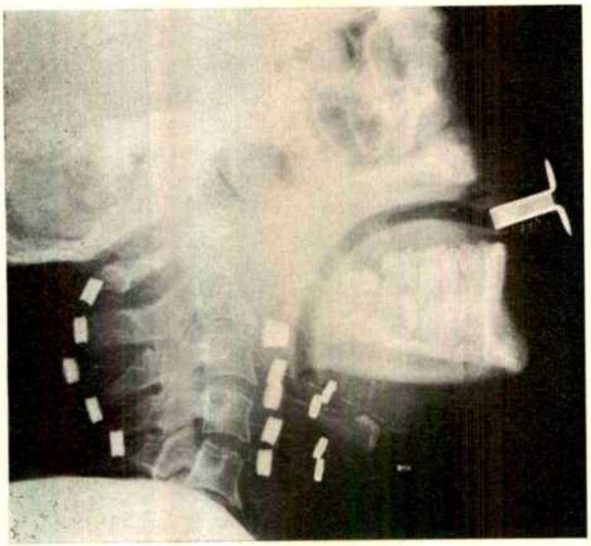

FIG. 3.

A check radiograph showing radio-opaque rubber washers at the skin surface. Lead washers are also visible.

The implant procedure is as described previously until all the outer nylon tubes are in position. The leading end of the wire mandrel is then passed along each protruding piece of nylon tube in turn to strengthen it and a rubber washer is slid from the mandrel, over the end of the tube and along it into position against the skin. There is very little frictional resistance to this operation if the nylon tube and rubber washers are made wet with saline beforehand, but once the rubber and tubing have dried the washer holds the tubing firmly in place by a radially applied pressure which does not distort or crush it. The rubber washer has thus taken the place of the block and pin and the final arrangement is illustrated in Fig. 2.

Early fears that the washers might slip during treatment have been allayed after 16 implants in which no evidence of movement has been seen. Check radiographs taken under normal conditions in the operating theatre show the barium sulphate-loaded washers clearly. An example is shown in Fig. 3. To have a clear marker at the skin surface for each tube helps when calculating the length of active wire which will be needed and delineates the implant clearly for dosimetric purposes.

It is reasonable to regard the washers as disposable items. They have been sterilized by immersion in chlorhexidine and by radiation and have been shown to be suitable for inclusion in a pre-sterilized theatre pack.

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Case reports

Multiple polyps of the small intestine: an unusual feature of multiple myeloma

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The various syndromes resulting from an abnormal proliferation or neoplasia of mature plasma cells or their immature precursors constitute the plasma cell dyscrasias. These may present as multiple myeloma (plasma cell myeloma), solitary myeloma, extra-osseous plasma cell myeloma, or plasma cell leukaemia.

We have encountered an unusual case of multiple myeloma in which a patient previously diagnosed by bone biopsy and immunoelectrophoresis, developed multiple non-obstructing polyps of the small intestine and at the oesophagogastric junction. On biopsy, these lesions had the classical histopathology pattern of multiple myeloma. This is the first case of myeloma polyps of the small intestine to be reported in the radiological literature.

CASE REPORT

A 72-year-old white female was admitted in 1972 with a painful mass in the mandible which was diagnosed as myeloma. Two years later, a mass in the right gluteal area appeared. This was biopsied, diagnosed as myeloma, and treated with radiotherapy. In May, 1974, she was re-admitted for evaluation of vague abdominal pain, nausea and vomiting, and for treatment of heart failure and hypertension. There was no evidence of gastrointestinal bleeding. Immunoelectrophoresis was compatible with multiple myeloma. Radiographic examination of the upper gastro-intestinal tract demonstrated multiple non-obstructing polyps throughout the small bowel (Fig. 1), including the duodenum (Fig. 2), with one rather large polyp at the oesophagogastric junction (Fig. 3). A barium enema was not done. Endoscopy and biopsy were performed and demonstrated the large polyps which proved to be extra-osseous myeloma (Fig. 4A and 4B).

The patient received a course of cyclophosphamide and vincristine sulphate and was discharged. She was later readmitted to another hospital because of myeloma and congestive heart failure and died. An autopsy was not performed.

DISCUSSION

While non-osseous presentation of plasma cell myeloma is unusual, hardly a site exists in which a plasmacytoma has not been reported Oberkircher *et al.*, (1972). Dolin and Dewar (1956) in reviewing 161 cases between 1905 and 1953 (and adding two of their own) found that a majority occurred in the oral cavity and upper respiratory tract. The gastro-intestinal tract was involved in less than 10% with myeloma occurring most frequently in the small intestine followed by the stomach, colon and oesophagus.

Myeloma rarely occurs in the small intestine. In our review of the literature, only 18 cases were found involving the small intestine and 50% involved the ileum (Esposito and Stout, 1945; Goldstein and Poker, 1966; Ingegno, 1954). Gastrointestinal myeloma may precede, accompany, or follow osseous involvement (Goldstein and Poker, 1966). Clinically, patients usually present with abdominal pain, bleeding and obstruction. Stricture is the predominant radiographic finding. Only two cases of myeloma of the duodenum have been reported (Goldstein and Poker, 1966)—both were obstructing lesions.

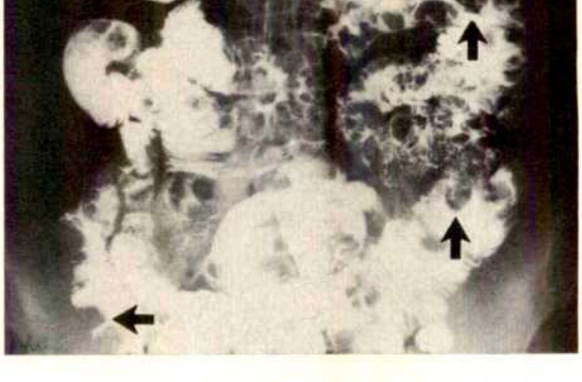

FIG. 1.

There are multiple polypoid lesions throughout the small bowel measuring 0.8 to 1.2 cm (arrows).

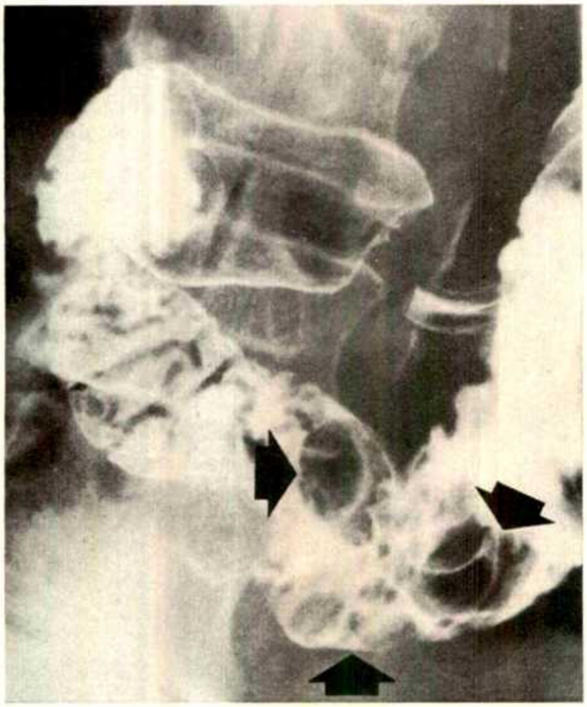

FIG. 2.
Several polypoid non-obstructing myeloma masses are present in the second and third portions of the duodenum (arrows).

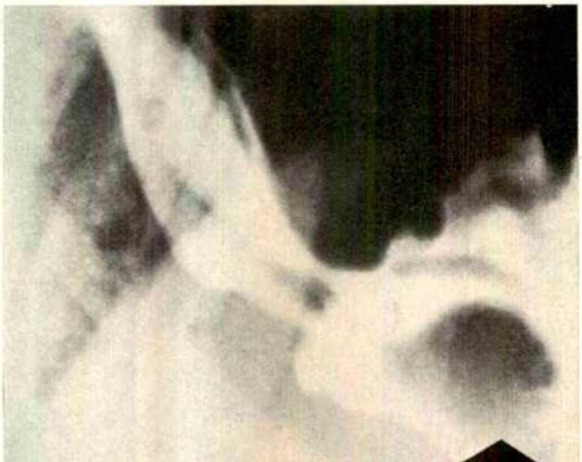

FIG. 3.
There is a polypoid lesion at the oesophagogastric region measuring 2.5 cm (arrow).

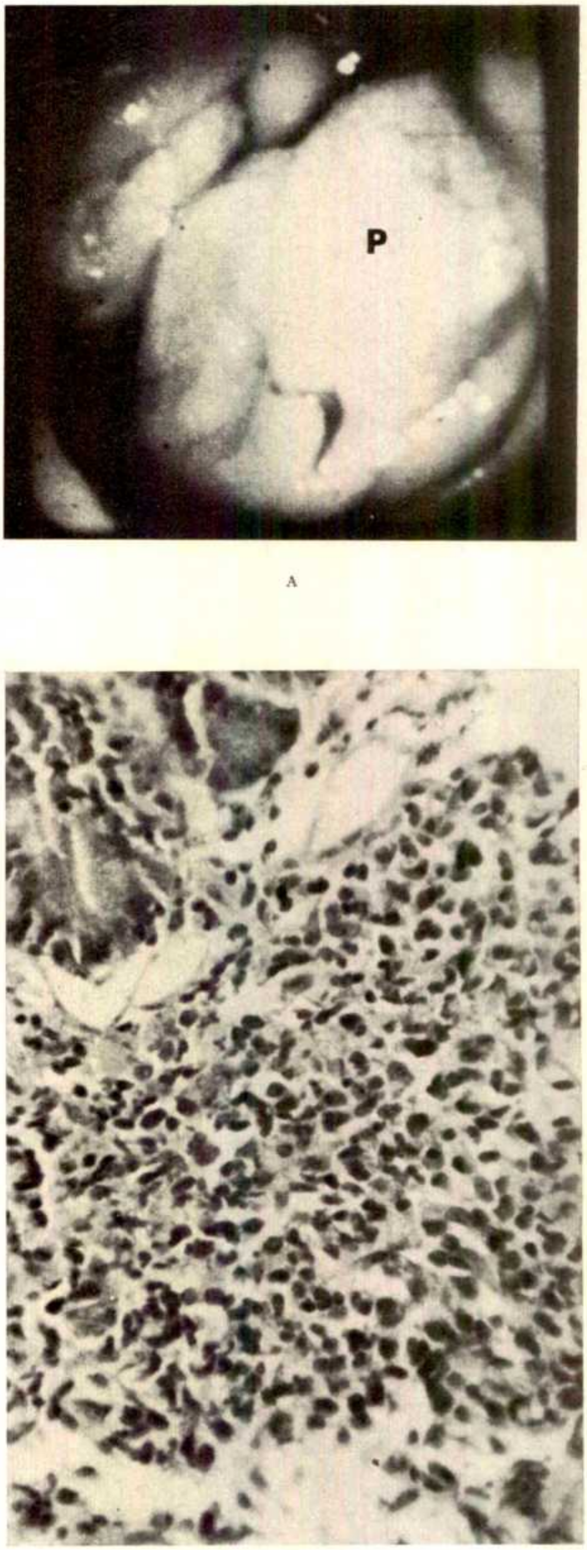

FIG. 4.
(A) Myeloma polyp as seen through the fibre-endoscope (P).
(B) Microscopic section of a duodenal polyp showing nests of small dark cells consisting of plasma cells and immature cells (plasma), some containing double nuclei. These cells are consistent with myeloma cells.

Although rare, extraosseous myeloma should be considered in the differential diagnosis of multiple polyps in the small intestine.

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Caroli's disease: an ultrasonic diagnosis

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Congenital dilatation of the intrahepatic bile ducts (Caroli's disease) was first reported in 1958 (Caroli *et al.*) and is usually diagnosed late in the patient's illness and seldom before operation (Watts *et al.*, 1974). Goddard (1974) could only find 16 previous case reports of the disease which attests to its rarity. Caroli (1968) has classified congenital intrahepatic cystic dilatation into two groups: first, a pure form not associated with hepatic cirrhosis or portal hypertension and second, a type associated with congenital hepatic fibrosis. There is probably some overlap but Watts *et al.* (1974) consider most cases belong to the first group. The radiological diagnosis of Caroli's disease has, in the past, proven difficult. None of the 15 cases collected by Mujahed *et al.* (1971) were diagnosed before surgery. With improved modern techniques in organ visualization, the pre-operative diagnosis has become easier and we report the following case which was confidently diagnosed by ultrasonography and confirmed by transhepatic cholangiography, thus rendering invaluable assistance to the surgeon.

CASE REPORT

A female of 19 years was first admitted to hospital in December 1975 because of increasing jaundice and rigors. Her clinical history was unremarkable except for her occupation as an assistant in a hospital sterilizing department and handling liver biopsy packs. Her total bilirubin was 5 mg% (conjugated level 3.8 mg%) and her alkaline phosphatase was 132 international units.

She was thought to have infective hepatitis but her jaundice never settled and a liver biopsy was compatible with cholangitis and biliary stasis. Her jaundice subsequently decreased, her symptoms improved and she was discharged.

In February 1976 her jaundice and rigors recurred. She was now pyrexial and her liver was enlarged by 3 cm. Her total bilirubin was 9.3 mg%. An isotopic technetium sulphur colloid scan showed a cold area in the A.I. portion of the right lobe. A Rose-Bengal scan was not performed. Her intravenous pyelogram was normal with no evidence of renal tubular ectasia.

Longitudinal and transverse grey-scale ultrasonograms, at high and low gain, were done with Diasonograph NE 4102 scan convertor, using a 2.5 MHz transducer. Four transonic lesions, varying from 2 to 5 cm in diameter, were found in the region of the porta hepatis (Fig. 1). Their cystic nature was confirmed by the absence of internal echoes at high and low gain and clear definition of their posterior walls. Their position was marked on the skin surface and longitudinal, sagittal scans were next done through the plane of these marks. The largest cystic structure was 5 cm in diameter and 12 cm in length (Fig. 2). An

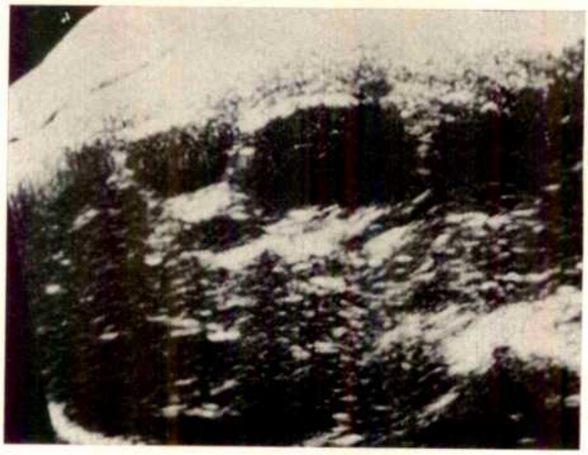

FIG. 1.

Transverse scan through the region of the porta hepatis showing four transonic structures.

undilated gall bladder of 3.6 cm diameter was identified independently and lateral to the largest cystic structure. Superior to the gall bladder and within the liver substance were three cystic lesions of 2–3 cms in diameter (Fig. 3). No biliary calculi were identified.

Taking the patient's age and clinical setting into account, a confident ultrasonic diagnosis of congenital cystic dilatation of the intrahepatic bile ducts was made.

After intensive treatment with antibiotics, her pyrexia settled and a transhepatic cholangiogram with a small gauge (23 mm) needle was done one week later. Undilated peripheral ducts were entered on the first attempt and

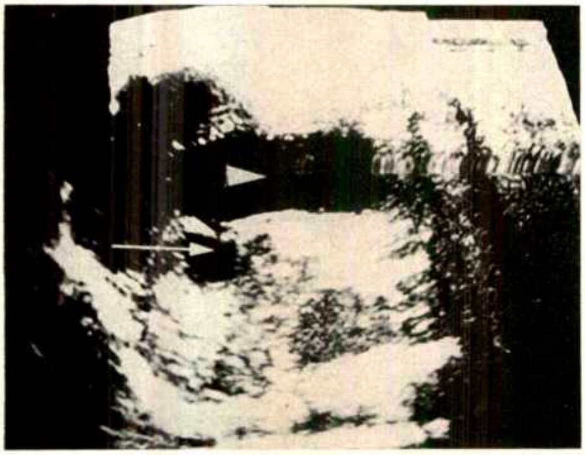

FIG. 2.

Longitudinal, sagittal scan 4 cm to the right of the midline showing a large cystic structure (arrowhead) projecting from the P.I. surface of the liver. A smaller cystic structure (arrow) is seen within the liver substance.

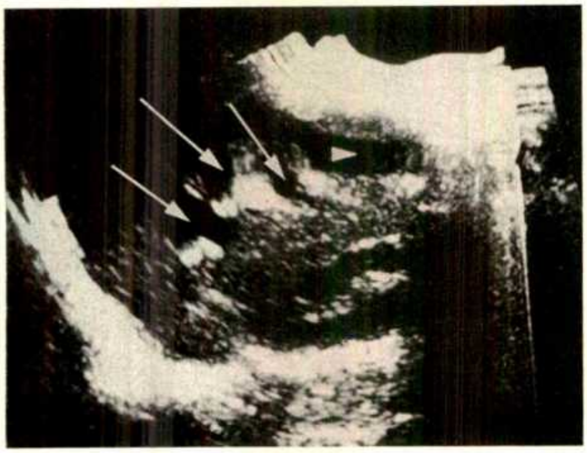

FIG. 3.

Longitudinal, sagittal scan, 7 cm to the right of the midline, showing an undilated gall-bladder (arrowhead). Three transonic structures (arrows) are shown within the liver.

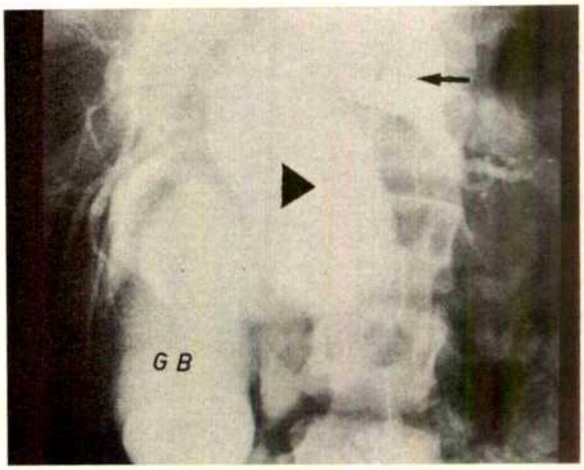

FIG. 4.

Percutaneous transhepatic cholangiogram showing several localized dilatations of the intrahepatic ducts of the right lobe of the liver (arrows). The choledochal cyst is well seen (arrowhead).

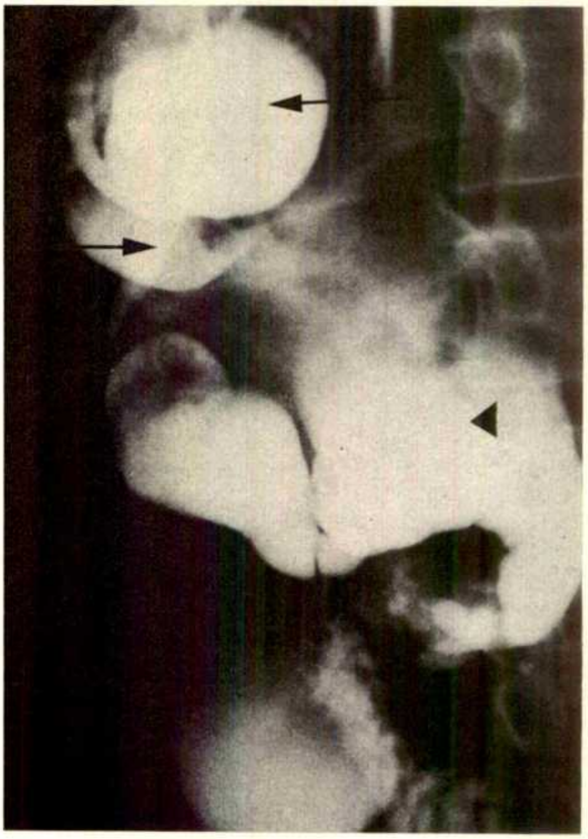

FIG. 5.

Transhepatic cholangiogram showing additional dilatations in the left intrahepatic ducts (arrows) and the large choledochal cyst (arrowhead).

contrast flowed into a localized dilatation. On further filling, several localized cystic dilatations were seen in both the right and left intrahepatic ducts (Fig. 4). There was also marked dilatation of the common bile duct in which there were many faceted gall-stones. Contrast flowed freely into the duodenum and the terminal portion of the common bile duct was undilated (Fig. 5).

Laparotomy confirmed the pre-operative radiological findings, and showed a 6 cm diameter choledochal cyst containing 12 calculi of varying size. The terminal common bile duct had a normal calibre. A choledochoscope was passed and the bilateral localized dilatations of the intrahepatic ducts well seen. The gall-bladder was full but not dilated. A cholecystectomy and Roux-en-Y choledocystjejunostomy were performed. The histology of the removed cyst showed biliary tract type mucosa with a thickened and fibrosed wall. The calculi consisted of cholesterol, bilirubin and a small trace of calcium.

DISCUSSION

Radiological diagnosis of Caroli's disease has, in the past, been difficult before surgery. Occasionally, mottling of contrast medium over the hepatic surface after cholangiography may indicate the intrahepatic cyst dilatations (Caroli and Corcos, 1964). This may be considerably enhanced by Logetronic technique (Caroli, 1973). Calculi may be visualized but the true nature of the underlying disease is not realized. Frequently, however, cholecystography, intravenous cholangiography and transhepatic cholangiography fail to opacify the ductal system (Foulk, 1970). Watts *et al.* (1974) consider operative cholangiography to be the most valuable test for the diagnosis, location and extent of the disease process, and mapping out the surgical approach.

Isotopic liver scanning may be helpful. A colloidal scan may show several decreased areas of uptake. If Rose-Bengal is then substituted, these areas may show increased uptake and stasis of the isotope. Angiography usually shows non-specific splaying of the vessels around the lesions and defects in the hepatogram.

The case presented demonstrates the value of ultrasonography in the early diagnosis of Caroli's disease. The finding of gross, localized cystic dilatations of intrahepatic bile ducts is highly suggestive of the disease. Suruga *et al.* (1969) reported the successful diagnosis of a choledochal cyst by ultrasonography but we have been unable to find a report of a successful diagnosis of Caroli's disease by this method.

Caroli's disease is probably congenital in origin and affects males and females equally. Patients usually present in childhood or young adulthood with a typical symptom complex characterized by recurrent abdominal pain, intermittent obstructive jaundice, and fever. Symptomatology is caused by stone formation due to bile stasis within the cysts, and by relapsing episodes of cholangitis; however, the disease may be asymptomatic (Foulk, 1970).

The dilated areas in Caroli's disease represent true ductal ectasias, which communicate freely with the biliary tree and contain bile. The dilatations may be widespread or localized, saccular, cylindrical or both. When the ductal ectasia is not diffuse it seems to be always localized to the left intrahepatic ductal system (Goddard, 1974).

A number of associations with Caroli's disease have been described and include hepatic fibrosis (Kerr *et al.*, 1961), renal tubular ectasia (Kerr *et al.*, 1962), intrahepatic lithiasis (Caroli and Corcos, 1964) and choledochal cyst. However, the association with choledochal cyst may well reflect obstructive dilatation rather than a primary error in intrahepatic ductal development (Kelly, 1971; Gots and Zuidema, 1970). In addition there appears to be an increased incidence of biliary tract carcinoma in patients with Caroli's disease (Watts *et al.*, 1974).

The usual surgical treatment for Caroli's disease is internal biliary drainage, especially choledochojejunostomy. Surgical intervention alleviates symptoms temporarily by removing calculi and re-establishing biliary drainage. Sooner or later infection recurs and often becomes uncontrollable with resultant liver abscesses and septicaemia, the usual cause of death. In 1968 Caroli considered that "this disease is not amenable to surgical treatment" which emphasizes the complexity of the surgical problem.

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The demonstration by scintigraphy of fractures in osteomalacia

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(*Received April, 1976 and in revised form December, 1976*)

Scintigraphy is an adjunct to radiology in the investigation of bone disease. It is of value in the diagnosis of neoplastic and inflammatory conditions and in the evaluation of radio- and chemotherapy. Its use in metabolic disease has been less well documented.

A patient with osteomalacia secondary to gluten sensitivity, in whom pseudofractures (Looser zones) were identified by bone scintigraphy, is reported.

CASE REPORT

A female, aged 56, gave a history of many years of joint pains and a period of diarrhoea 18 months prior to admission. A barium enema was reported to be normal. She was admitted for investigation of right groin pain following a trivial leg injury and volunteered a recent story of pale offensive stools and pains in both arms and shoulders. There was no history of trauma and no relevant past or family ailments.

On examination she was thin (height 165 cm, weight 44 kg) and looked pale. There was tenderness in the right groin during examination of the hip but no other abnormalities were observed. Investigations confirmed the suspected malabsorption. Barium follow through studies showed flocculation, segmentation and dilution of the contrast; no structural defect was seen in the bowel. A jejunal biopsy showed almost total villous atrophy. Radiographs demonstrated pseudofractures of the neck of the right femur, both superior and inferior pubic rami, and of the right 6th rib posteriorly (Fig. 1).

A bone scan using 10 mCi of technetium-99m-polyphosphate (TcPP) confirmed the radiological lesions and, in addition, identified nine other sites of markedly increased uptake: seven in the ribs and one each in the tip of the right acromion and in the left glenoid fossa. There was an unusually high ratio of activity in bone to soft tissue background (Fig. 2).

Her progress on a gluten free diet supported the diagnosis of osteomalacia secondary to gluten sensitivity malabsorption.

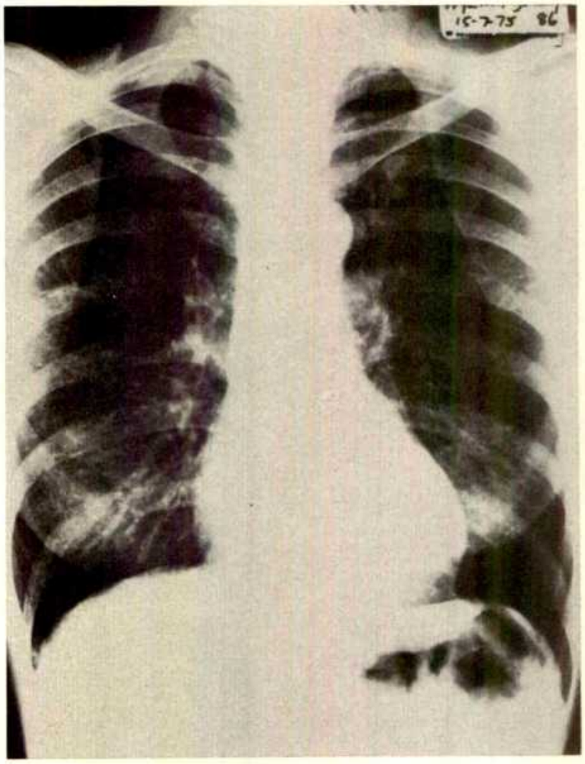

FIG. 1.

Chest radiograph: There is a fracture of right 6th rib.

DISCUSSION

Bone scintigraphy with various radionuclides, and especially with TcPP, is of value in the diagnosis of traumatic, neoplastic, inflammatory and infectious bone and joint disease. Its use in metabolic conditions has been less well documented. In particular, fractures in osteomalacic patients without renal disease have not been described.

The confirmation of Looser zones in our patient, and their demonstration in sites where there was no overt radiological change, is analogous to the identification of scaphoid fractures (Lutkin and Burwood, 1977) and stress fractures (Burry and Maisey, 1975) by scintigraphy where early radiographs may appear normal.

In a case report (Massachusetts General Hospital, 1975) of primary hypophosphatemic osteomalacia, a fracture was demonstrated radiologically in a metatarsal bone. This site was not included in the illustration of the diphosphonate bone scan. Two foci of increased uptake in the ribs were probable pseudofractures but had not been identified on the chest radiograph.

Rosenthall and Kaye (1975) reported an anorexic patient with osteomalacia and an abnormal scan. Their discussion was directed to the high ratio of activity in bone to soft tissue. They did not comment upon a very definite focus of high activity in each calcaneus. It is suggested that these foci may have represented pseudofractures of the calcanei.

An avidity of bone for TcPP was evident in the present case. This phenomenon has been observed in renal osteodystrophy (Sy and Mittal, 1975), Paget's disease of bone, osteomalacia and, less consistently, in hyperparathyroidism (Rosenthall and Kaye, 1975). A possible mechanism has been discussed by Kaye *et al.* (1975) who postulate, from animal studies, that TcPP is as strongly bound by immature collagen (in the unmineralized osteoid) as by mineralized bone. Paget's disease, osteomalacia and hyperparathyroidism may be associated with excessive hydroxyprolinuria—a marker of increased collagen turnover and hence of active bone disease, which may explain the high ratio of bone to soft tissue seen in these conditions.

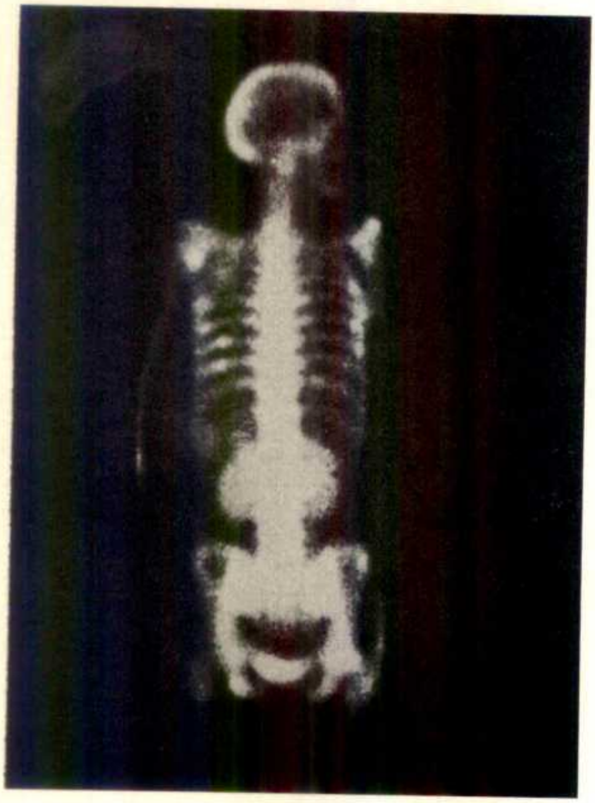

Fig. 2.

Posterior view of bone scan: there are multiple areas of increased uptake, especially in ribs, right acromion and left glenoid.

It is possible that this ratio has a relationship to the severity of the bone disease. In renal osteodystrophy there is a correlation between the ratio of bone to soft tissue and both the duration of dialysis and the alkaline phosphatase level (Sy and Mittal, 1975).

A second patient in Brighton with a less florid biochemical picture of osteomalacia and a shorter history showed a ratio of bone to soft tissue at scintigraphy that was within normal limits.

The demonstration by scintigraphy of multiple foci of high activity usually implies multiple secondary deposits. The scan must be reviewed in relation to all clinical and diagnostic findings in order that a correct interpretation can be made. Symmetry of lesions such as was seen in this patient's pubic bones may be particularly helpful in supporting a diagnosis of osteomalacic fractures.

Conclusion

It is suggested that scintigraphy with TcPP is of value in the demonstration of pseudofractures in osteomalacia and that such lesions may be identified when radiographs are normal. Comment is made on the differential diagnosis of multiple foci of high activity.

Addendum

Another patient, a lady aged 67, receiving anticonvulsant medication and with a past history of a partial gastrectomy, developed bone pain and tenderness in her left heel. Osteomalacia was suspected and confirmed biochemically. Radiographs showed severe demineralization in all bones of the pelvis, legs and feet but no evidence of any fractures. A technetium polyphosphate bone scan revealed an area of high uptake in the left calcaneum. There was symptomatic and biochemical reversal with appropriate therapy for her osteomalacia.

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Book reviews

Computer Applications in Radiation Oncology. Edited by Edward S. Sternick, pp. xxix+559, 1976 (Hanover, New Hampshire, U.S.A., University Press of New England), £15·00.

This volume records the Proceedings of the Fifth International Conference on the Use of Computers in Radiation Therapy, held at Dartmouth College in Hanover, New Hampshire, U.S.A. Physicists, radiotherapists, computer scientists and manufacturers' representatives, numbering 140 altogether, were invited to meet in August 1974 for six days to consider the theme "Preparing for the Next Five Years".

The organizers asked the conference to consider, within the context of this general theme, two questions: (1) what should the computer package consist of in terms of both hardware and software, (2) what should the priorities be in different stages of development? The following applications of the computer were selected for scrutiny: (a) control of patient flow and records, (b) automation and verification of therapy equipment, (c) treatment planning systems, (d) cell population models and parameters.

The volume reproduces the 35 invited papers read at the sessions devoted to these applications, together with the discussion that was held after each session. The final section of the proceedings contains 22 papers that were not read, the abstracts of all these papers and an index of authors.

Did this conference answer the questions posed by the organizers? Each participant will have formed his own opinion on that. The rest of us who are interested in this field will have to rely on this volume. Does it contain the answers?

In seeking information from these papers it must be remembered that 35 of them originated from North America, 11 from continental Europe, and ten from the United Kingdom. There was one contribution from Japan. Therefore, whilst the flavour of the volume is distinctly North American, work being done in Western Europe is represented and it is possible to compare the progress on each side of the Atlantic.

A further point that must be realized is that less than 10% of the participants were clinicians. Once or twice in the discussion somebody remarked that the only real objective for computer-based activities is the improvement in the care of the individual patient.

Some contributors acknowledged that devising systems to be utilized in hospitals is not straightforward. Reference is made to "building upon the ashes of previous systems". One wonders what caused the failure of these previous systems. Did they provide any answers or was it that they provided the wrong answers? How certain can one be now that the new system provides the correct answer?

In discussion one or two participants asked how the benefit to the patient could be determined. But most of the participants seemed to be satisfied that the use of the computer in radiotherapy was justifiable judged in terms of expenditure of money and of man-hours. Looking at the subjects that have been discussed, there can be little doubt that the computer has been a catalyst during the past ten years in the fields of dosimetry, medical records, radiobiology and analysis of the results of treatment. At conferences such as these, for most of the time it has not been the function of the computer that has been presented and discussed, for the computer has only been the tool, but the basic and derived concepts in dosimetry, radiobiology and clinical data analysis. It must, however, be admitted that without this tool much of the work that is presented in a volume such as this would never have been done.

The reader has to turn to the final panel discussion to learn how the conference judged whether it had answered the questions posed by the organizers. No real answers emerge. C.R.E., elimination of human errors, training and education, are indicated as areas which will benefit in the next five years by application of the computer.

This volume will be useful to anyone contemplating the application of a computer to their field of special interest if they are unfamiliar with E.D.P. For those already aware of the advantages and disadvantages of computer applications these proceedings will represent the "state of the art" as it was in early 1974.

D. N. Edwards.

Magnification Radiography. By S. Takahashi and S. Sakuma, pp. 110, 1975 (Springer-Verlag) $33.60.

The Japanese have, for sometime, been developing fine focus X-ray tubes and associated equipment for general radiography and fluoroscopy at magnification, and this book gives a first-hand account of the current state of the art. The physical principles underlying the technique are well described and documented; equipment by Toshiba and Hitachi transforms the principles into clinical practice.

Extra detail revealed by the magnification technique is portrayed by comparison of "normal" with magnification radiographs in a number of examples varying from an excised toe to pulmonary arteriography. Exposure factors for a 0.05 mm tube used to obtain X4 magnification radiographs in these examples seem very reasonable but the clarification of image detail which one always intuitively expects from such an elaborate procedure is somewhat disappointing. Magnification radiography of thick parts of the body still suffers from unwanted scatter. The use of contrast media partially compensates for this impairment of resolution and does enable good images to be obtained: however at this level of comparison one always begins to wonder if a small change in normal technique might produce equivalent results.

B. L. Reece.

1977, *British Journal of Radiology*, 50, 372–375

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(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

SCREENING FOR BREAST CANCER

In the October issue of the *Journal* on p. 818 the statement is made, "Although the New York experience suggests that women under the age of 50 do not benefit from screening, over half the cancers found in the West London study were in women under 50 years of age". Reference to the report on this study by Chamberlain *et al.* in the November 22, 1975, *Lancet*, eight such cancers were found and the statement is made on p. 1027 of that issue, "the large number of cancers detected in women aged 40 to 49 merely reflects the fact that most women attending the clinic were in this age group".

The statement in the *Journal* would thus appear to be meaningless, and one wonders what purpose it was meant to serve.

Yours, etc.,
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THE EDITOR—SIR,

SCREENING FOR BREAST CANCER

I am grateful to you for bringing Dr. Brown's letter to our attention and I agree that the paragraph is not quite as explicit as it could be. I hope that the following remarks may clarify the problem.

Recently there have been recommendations that mammography should be restricted to women over 50 in breast cancer screening programmes. This is based on evidence from the H.I.P. New York Study that the reduction in mortality from breast cancer due to screening was less marked in women under 50, and on the fear of radiation induced cancer from mammography. The most recent figures from the West London Study show that for the 40–50 age group 30.7% of the cancers were found by mammography alone and a further 30.7% by clinical examination and mammography. In the New York study 19.4% of cancers in this age group were found by mammography only and 19.4% by clinical examination and mammography. As the lowest case fatality rate occurred in breast cancer cases positive only on mammography, I suspect that the less favourable outlook for the younger age group in the New York Study may be related to the lower proportion of cancers discovered in the under 50s by mammography alone.

There has been an improvement in mammography techniques in recent years with the advent of X-ray units and screen/film combinations specifically designed for mammography and we feel that the West London results indicate that more cancers are being found in younger women with the Medichrome film/rare earth screen combination. These techniques minimize the radiation hazard and it should be remembered that no increase in breast carcinoma has yet been demonstrated in female Japanese atomic bomb survivors who received a dose of more than 90 rad, and were over the age of 35 at the time of irradiation.

In England and Wales breast cancer is the commonest cause of death in women aged 35–54 and it would be sad if the possible benefits of screening were to be denied to this age group before the latest mammographic techniques are fully evaluated.

Yours, etc.,
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THE EDITOR—SIR,

THE SMALL BOWEL BARIUM FOLLOW-THROUGH VERSUS JEJEUNAL BIOPSY IN THE DIAGNOSIS OF COELIAC DISEASE

Masterson and Sweeney (1976) recommend a barium follow-through as the initial investigation of patients suspected of having coeliac disease. The age of their patients is not stated; they may well have been adults but I think few paediatricians will agree with their statement.

Many screening tests have been advocated in the hope of avoiding jejeunal biopsy but an accurate diagnosis can only be made on histological grounds. The full diagnostic criteria for coeliac disease should be the demonstration of an abnormal small intestinal mucosa by biopsy followed by a histological response to a gluten-free diet and finally the demonstration of a histological relapse following a gluten challenge.

Masterson and Sweeney point out that the radiological findings are usually non specific and although a flat jejeunal mucosa is characteristic of coeliac disease there are other conditions in children such as gastroenteritis, cow's milk protein intolerance and giardiasis which may produce the same appearance. For these reasons reinvestigation as outlined above is justified in order to establish the diagnosis of coeliac disease with certainty as this will necessitate a gluten-free diet for life.

A jejeunal biopsy can be done as a day case and "costly hospitalization" is not needed and I suggest that it is more simple to perform than a barium follow-through examination. In children it is a safe procedure if the port hole of the capsule is of the correct size. Visakorpi (1970) reports only eight perforations in 4937 biopsies. A biopsy has the further advantage that when indicated the disaccharidase activity of the small intestinal mucosa may be measured and often observations such as immunological studies are possible. Furthermore, during the procedure a sample of duodenal juice may be obtained either for culture or to exclude giardiasis.

For these reasons if a child is suspected of having coeliac disease then the initial investigation should be a jejeunal biopsy rather than radiological studies and the diagnosis should not be made or treatment started without this investigation having been performed.

Yours etc.,
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THE EDITOR—SIR,

BARIUM FOLLOW-THROUGH AS THE INITIAL INVESTIGATION OF PATIENTS SUSPECTED OF HAVING COELIAC DISEASE

We agree wholeheartedly with the view of Dr. Husband that an accurate diagnosis of coeliac disease can only be made on histological grounds. It was not our contention that barium follow-through examinations should supersede jejunal biopsy in arriving at a definitive diagnosis but rather that because the findings at barium examination correlate so closely with alterations in the jejunal mucosa and because it is a non-invasive technique with no attendant morbidity it is the method of choice in screening patients suspected of having coeliac disease.

If the barium examination is normal then the likelihood of the patient having coeliac disease is small (approximately 5% in our series) and further investigation such as jejunal biopsy (which as Dr. Husband points out is attended by a real, albeit small, danger of bowel perforation) may be avoided. No one would deny the necessity of mucosal sampling in cases with abnormal findings on barium follow-through. The lack of specificity of the radiological changes dictates that a definite diagnosis be reached by other methods.

With the single exception of a 13-year-old patient with treated coeliac disease all our patients were adults; the average age being 37 years.

Yours, etc.,
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THE EDITOR—SIR,

RBE VALUES FOR CALIFORNIUM-252; OER OF HYPOXIC CELLS

I am surprised that Kal (1976) and Hall and Rossi (1976) seem to assume that *single* values for the RBE of ^{252}Cf can be derived from all the various sources in the literature. Hall and Rossi (1976) correctly state that "At any given dose-rate, the RBE varies significantly with the biological system or end-point studied". They must know that RBE values may also vary with dose level, particularly when two dose-response curves are being compared which do not have the same shape. Examples of these were actually illustrated by Hall and Rossi (1975) in their review article but single RBE values were still assumed.

In that review they took exception to the Chinese hamster (CHO) cell survival data from Manchester (Nias *et al.*, 1973a) because the ^{252}Cf dose-response of aerated cells could be fitted to a shouldered survival curve while the response to ^{60}Co fitted pure exponentials. We accepted that there were radiobiological conceptual difficulties in this computer fitting of our data and discussed the alternative survival curves indicated by the data. Unfortunately, Hall and Rossi (1975) chose to use these computed D_0 values to calculate a single RBE. After correction of our value of 6.7 for the 33%γ contribution, they calculated an RBE of 8.04 for ^{252}Cf neutrons alone at our total dose-rate of 15 rad/hour and used this value in their graphical presentation (although an accompanying table erroneously gave an RBE of $\sim$10 and a dose-rate of 20 rad/hour).

It seems to me that if a single RBE value must be chosen from a number of such cell survival studies it would be more appropriate to use the actual survival data and to make the comparison around the 5–10% survival level, away from the complication of a possible shoulder on a fitted curve. We actually quoted an RBE of 5.1 at the 5% level (Nias *et al.*, 1973a) and this figure would be corrected to an RBE of 6 for ^{252}Cf neutrons alone—a value which would now fit precisely on the graph of Hall and Rossi (1975). There would be no need for Kal (1976) to have omitted our data altogether.

The omission of scientific data from reviews should be a cause for some concern. The criticism by Kal and Barendsen (1976) of many oxygen enhancement ratio (OER) values determined at low dose-rates will need careful consideration. Since such data were a part of the ^{252}Cf study discussed above, it seems opportune to discuss the technique used for the protracted hypoxia. We investigated cell survival following such hypoxic storage and found an exponential decrease to 10% after 45 hours with CHO cells (Nias *et al.*, 1973a) and after 30 hours with HeLa cells (Nias *et al.*, 1973b). I am well aware that this technique of cell crowding may have other effects upon the cells, in addition to hypoxia. The fact remains that the technique for cellular hypoxia was precisely the same for both the ^{252}Cf and the ^{60}Co irradiation and that the period of hypoxia was also the same (up to a total of 30 hours) because we assumed an RBE of 5.

Whatever the artefacts of this system, therefore, our observation of a lower OER with ^{60}Co irradiation at 100 rad/hour than with ^{252}Cf at 15 rad/hour is based upon a comparison where the experimental conditions were identical. On the other hand, we have not yet performed the hypoxic storage experiment for high dose-rate studies, as suggested by Kal and Barendsen (1976); so the question whether our low values for OER with low dose-rate irradiation are artefactual remains open.

Yours, etc.,
A. H. W. NIAS.

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THE EDITOR—SIR,

THE OER AT LOW DOSE-RATES

I would like to comment on the letter by Drs. Kal and Barendsen which appeared in the December issue of THE BRITISH JOURNAL OF RADIOLOGY (Kal and Barendsen, 1976).

Basically I agree with Dr. Kal's thesis. In his summary of OER values for low dose-rate γ-rays, collected from the literature (Fig. 1), the very lowest of all was taken from one of our early publications in this journal (Hall *et al.*, 1966). In these experiments HeLa cells, growing on plastic dishes, were made hypoxic by gassing them for nine hours with nitrogen and 5% CO_2. These experiments were performed in the early 1960s, before it was appreciated that the radiation sensitivity of cells varied so dramatically with phase in the cell cycle, and before it was realized that plastic dishes contained dissolved oxygen. Consequently, I would be the first to admit that the reported OER of 1.5 is to some extent an artefact. Later experiments, by ourselves and others, do not suffer from these problems. On the plot by Drs. Kal and Barendsen there were two points from more recent work of this laboratory, one for *Vicia* seedlings at 46.9 rad/h and one for mammalian cells at 50 rad/h (Hall and Fairchild, 1970; Hall *et al.*, 1974). Both yielded OER values close to 2, which is still significantly lower than the OER for acute X or γ ray exposures. Neither of these experiments suffer from the deficiencies of the earlier work, namely the piling up of cells in a sensitive phase of the cycle, and/or the problem of

1977, *British Journal of Radiology*, *50*, 374–375

oxygen contamination from plastic. I would be interested to hear the views of other experimenters whose data are represented in Dr. Kal's summary.

This reduction in OER for γ-rays at the low dose-rates characteristic of interstitial implants is modest, but not negligible. Implants may not be the poor man's neutrons, as they were once described, since these particles characteristically have an OER closer to 1.6. However, they may be the poor man's pions or heavy ions, since current data indicate that by the time the Bragg peak is spread out to cover a 10 cm volume, the average OER for these charged particles is in excess of 2.

At the present time there is something of a renaissance in the use of low dose-rate interstitial implant therapy. To put things into perspective, it is my view that other factors, such as the intense non-uniform dose distribution and reoxygenation taking place during protracted exposures, are much more likely to contribute to the success of implants than the slightly lowered OER. Nevertheless the lowered OER is not completely negligible, and it is a sobering thought if a simple implant can match, for both OER and dose localization, the most sophisticated and expensive pion or heavy ion treatments.

Yours, etc.,
E. J. HALL,
Professor of Radiology

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THE EDITOR—SIR,

COMPUTERIZED TOMOGRAPHIC SCAN TERMINOLOGY

Dr. Rhys Davies, amongst others, has drawn attention to the confusion which surrounds the terminology for both transmission and emission imaging techniques. Terms such as CAT and PETT can be meaningless to the uninitiated. Indeed, the acronym conscious might be tempted to embody all such terms in Radiation and Transmission Systems (RATS).

A simple generic title followed by a descriptive term related to the equipment in use is all that is required. Computed Tomography (Emiscan) has been employed in Manchester for the brain and the body since 1973. The term is accurate and readily understood by all concerned, including the patient.

Yours, etc.,
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THE EDITOR—SIR,

DUODENAL VIZUALIZATION AS AN AID TO THE INTERPRETATION OF PANCREAS SCINTIGRAMS

The recent review of pancreas scintigraphy by Agnew *et al.* (1976) serves to emphasize how much this procedure still relies on the expertise of the person interpreting the scintigram. One point, which was not discussed, is the relationship between chemically synthesized ^{75}Se-L-selenomethionine and the biosynthesized product. It has been claimed that the synthetic product produces better results. In a retrospective evaluation of pancreas scintigrams prepared using chemically synthesized ^{75}Se-L-selenomethionine, we did indeed find a higher degree of visualization of the pancreas than has been reported for the biosynthetic product (Cox *et al.*, 1977). Nevertheless many problems were still encountered in interpreting dubious scintigrams, primarily because in most cases pancreas uptake is reduced and it is difficult to distinguish the pancreas activity from selenomethionine activity in the gastrointestinal tract.

FIG. 1.

Upper left: lower border of liver visualized with ^{99}Tc^{m} phytate. Lower left: ^{75}Se-L-selenomethionine scintigram with liver, pancreas and intestinal accumulation of activity. Upper right: visualization of proximal small intestine and stomach with oral ^{99}Tc^{m} colloid. Lower right: superposition of colloid scintigram on selenium scintigram to demonstrate intestinal selenium uptake and localize pancreas associated activity.

In such cases we have found it helpful to visualize the proximal gastrointestinal tract by giving the patient 0.5mCi ^{99}Tc^{m} colloid orally after the pancreas image has been recorded (Tjen *et al.*, 1977). The resulting visualization of the stomach and duodenum clearly indicates where the head of the pancreas should be located and assists in identifying regions of selenomethionine uptake associated with the intestines.

An example is shown in Fig. 1. The upper left scintigram shows the lower border of the liver visualized with ^{99}Tc^{m} phytate. The lower left scintigram shows pancreas, liver and intestinal ^{75}Si-L-selenomethionine. The upper right scintigram was prepared directly after the selenomethionine scintigram after oral administration of ^{99}Tc^{m} colloid and clearly shows activity in the stomach and small intestine. Superposition of this scintigram on the selenomethionine scintigram, lower right, demonstrates the selenium activity associated with the intestine and clearly shows the head of the pancreas lying in the curve of the duodenum.

Yours, etc.,
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H. S. L. M. TJEN,
W. B. VAN DER POMPE.

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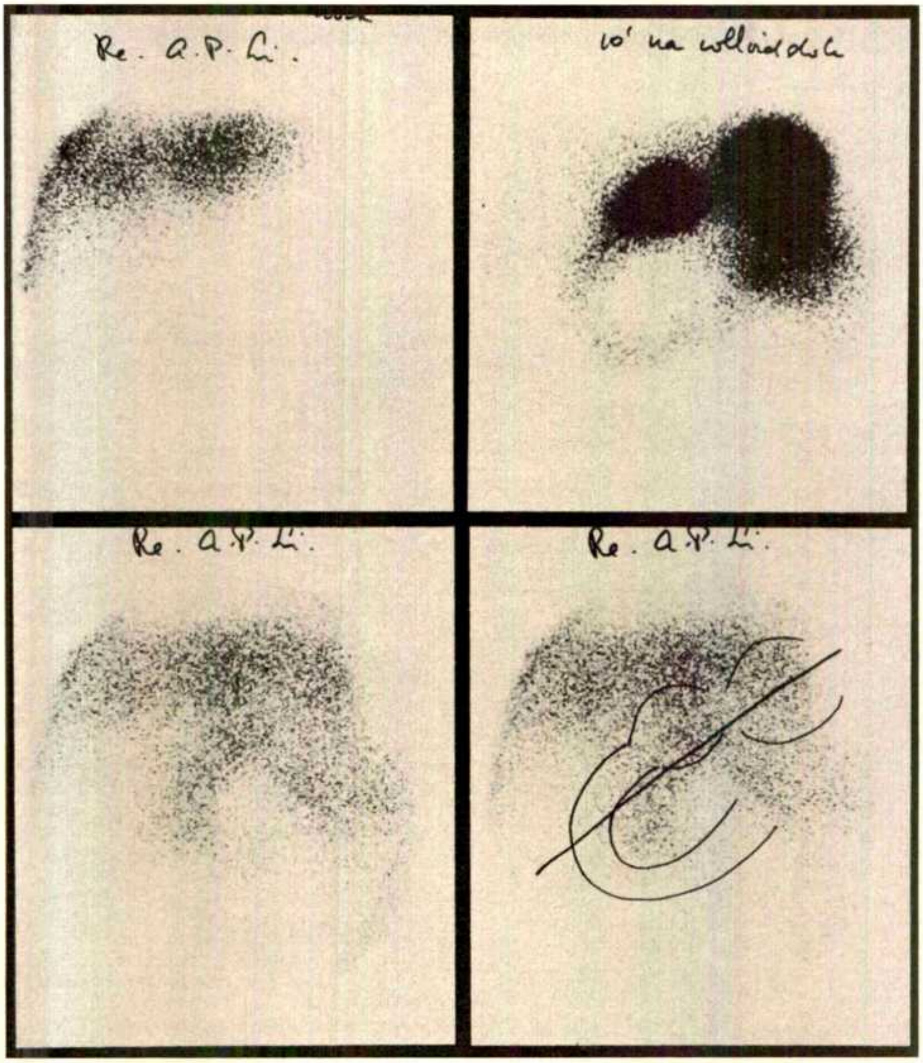

Fig. 1.

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Proceedings of The British Institute of Radiology

A spinal evening

Abstracts of papers presented at a meeting held on October 7, 1976 at The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG

Whither myelography, by R. G. Grainger.
The whole body scanner in spinal investigations, by I. Isherwood, R. A. Fawcitt, J. Nettle, J. W. Spencer and B. R. Pullan
Practical applications of selective spinal angiography, by B. E. Kendall.
Spinal phlebography: clinical applications, by I. F. Moseley.

WHITHER MYELOGRAPHY

By R. G. Grainger

Department of Radiology
The Royal Hospital, West Street, Sheffield S1 3SR

The recent introduction of water-soluble contrast media solutions with reduced neuro-toxicity and greatly reduced osmolality has stimulated a complete re-appraisal of the optimal method of myelography. Meglumine iocarmate (Dimer X) is the meglumine salt of bi-valent iocarmic acid (6 iodine atoms/molecule). Metrizamide (Amipaque) is a non-ionic substituted amide of metrizoic acid (3 iodine atoms/molecule). Both of these products produce lumbo-sacral and lower dorsal myelograms of far greater diagnostic value than oil myelography (Myodil). The main diagnostic advantage is in suspected lumbar disc prolapse with nerve root compression. The accuracy of positive myelographic findings is 95% proven at surgery. The risk of adhesive arachnoiditis is considerably less than with oily agents and is probably very small. Cervical myelography (Metrizamide is advised) is a more difficult procedure with water-soluble products and its advantages over oil cervical myelography have not yet been fully assessed.

THE WHOLE BODY SCANNER IN SPINAL INVESTIGATIONS

By I. Isherwood, R. A. Fawcitt, J. Nettle, J. W. Spencer and B. R. Pullan

Departments of Diagnostic Radiology and Medical Biophysics
University of Manchester

Two hundred patients have been examined on the EMI CT 5000 Whole Body Scanner.

Studies have been made of disarticulated and cadaver spine to identify (a) normal anatomical features in cross sectional slices of 13 mm depth and (b) the effect of normal and abnormal curvature of the spine on these features.

Patients have been studied by computer tomography following lumbar injection of Metrizamide. The distribution, flow pattern and dilution of Metrizamide have been investigated in detail in ten patients. This preliminary study suggests that Metrizamide (a) is necessary in the spinal canal to visualize the neural axis and pathological processes which affect it; (b) may appear in the subarachnoid space of the head and upper cervical spine in one hour; (c) enters the extracellular space of the spinal cord in the first hour; (d) achieves a uniform diffusion and dilution pattern in the subarachnoid space and spinal cord from three to six hours; (e) may concentrate in a second compartment, possibly intra-cellular, from three to six hours.

The effect of spectral filtering by Metrizamide on the attenuation values of the spinal cord has been modelled and shown not to be significant at the anticipated dilution of contrast medium in the cerebrospinal fluid space of the spinal canal.

PRACTICAL APPLICATIONS OF SELECTIVE SPINAL ANGIOGRAPHY

By B. E. Kendall

National Hospital for Nervous Diseases
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Angiomas involving the spinal cord are usually diagnosed by myelography but occasional cases do occur in which myelographic appearances are non-specific, or are normal in which the diagnosis has been made by selective spinal angiography. Selective angiography is necessary prior to surgery or therapeutic embolism to confirm the angioma and to localize the site of arteriovenous shunting, its relationship to the surface of the spinal cord and the meninges as well as to show the supplying arteries and their relationship to the blood supply of the spinal cord.

Spinal ependymomas and astrocytomas usually have a similar vascularity to that of the normal spinal cord and spinal angiography gives disappointingly little important information in these tumours which together constitute over 90% of intramedullary neoplasms. Haemangioblastomas which constitute only 5% of intramedullary tumours show a characteristic hypervascular blush and it may be useful for the surgeon to know the precise site of such a hypervascular tumour nodule in relationship to the spinal cord and its blood supply and especially the position of such a nodule within a large cyst, which is a not uncommon component of such tumours. Haemangiomas may be suspected prior to angiography from clinical features in cases of Hippel Lindau disease and on myelography where they are relatively more frequently associated with enlarged blood vessels than the more common tumours.

The variable origin of the arteria radicularis magna makes it desirable to identify its origin in conditions in which intercostal and upper lumbar arteries may be interrupted during surgery. These conditions include severe scoliosis, masses such as prolapsed thoracic discs and some extra-axial tumours, angiomas of vertebral bodies and aneurysms and stenoses of the aorta especially if the latter are associated with symptoms suggesting ischaemia of the spinal cord.

Unequivocal findings of occlusion of the arteria radicularis magna or anterior spinal artery may occasionally be useful in the distinction of ischaemic myelomalacia from transverse myelitis. However, this may require an extensive study and recanalization may make it impossible to recognize ischaemic pathology on angiograms. Most clinicians do not consider that angiographic confirmation of such diagnoses are justifiable, since it leads to no specific treatment.

Proceedings of The British Institute of Radiology

SPINAL PHLEBOGRAPHY: CLINICAL APPLICATIONS

By I. F. Moseley

Lysholm Radiological Department, National Hospital
Queen Square, London WC1 3BG

Retrograde transfemoral catheterization and injection of the epidural venous plexus is a relatively simple and safe procedure which can be carried out under local anaesthesia without undue discomfort to the patient. It does not necessarily require admission to hospital.

The technique is of proven value in the investigation of cases of possible lumbar disc prolapse in which other procedures yield negative or equivocal results. Since the anteriorly-placed veins lie in close proximity to the intervertebral discs, they may reflect minor or lateral protrusions which are not producing changes detectable at radiculography. This is particularly true at the lumbosacral disc, where the theca is often separated from the disc space even in the absence of disc disease.

Useful information may also be gained about the extent of intraspinal and paraspinal tumours and of spinal canal stenosis. The technique may also be extended to the cervical region.

Book review

Hodgkin's Disease. Edited by Mortimer J. Latcher, pp. xv+492, 1976 (John Wiley & Sons), £14·00.

This recent addition to the already formidable number of books devoted to a relatively uncommon disorder is essentially an account of Hodgkin's disease as it is understood and managed at the Memorial Centre, New York, where 24 of the 36 contributors are centred. In 27 chapters a multitude of aspects are discussed in considerable depth, providing a wealth of material for anyone interested. And nowadays there are very few medical practitioners who disclaim interest in Hodgkin's disease.

For the radiotherapist there are two chapters describing treatment techniques in considerable detail. It is particularly interesting to note that one of these chapters deals solely with techniques developed using Cobalt 60 units, because in some centres it is claimed that effective total node irradiation can be given safely only with a linear accelerator. Four chapters cover most aspects of those cytotoxic drugs at present commonly used in the treatment of Hodgkin's disease. For the surgeon there are three chapters dealing with the indications for and the techniques and complications of diagnostic laparotomy. Separate chapters cover other diagnostic procedures commonly used in the staging of Hodgkin's disease. Others are devoted to aetiological, epidemiological and pathological aspects of the disease and its complications.

In a multiple-author book of this type it is relatively easy for a reviewer to discover some apparent imbalance. A whole chapter devoted to "Acute Respiratory Failure in Patients with Advanced Lymphoma" may be considered excessive. When a patient has the misfortune to reach such an advanced stage with uncontrolled disease, acute respiratory failure may be more properly regarded as a merciful release than an exercise in suspended animation in an intensive therapy unit. Another minor criticism is that some chapters refer at length to other lymphomas rather than Hodgkin's disease.

The introduction to Chapter 12 is unnecessarily emotive and scientifically inaccurate, conveying the idea that combination chemotherapy and combined modalities of treatment are only now leading to significant cure rates in this "dread disease". For many years, Hodgkin's disease has been one of the most curable of all forms of cancer and the excellent results at present obtainable with combination chemotherapy when the disease is widespread were first reported in 1970, since when they have remained unchanged. A further criticism of this chapter is that it is stated that substitution of Vinblastine for Vincristine in MOPP reduces the complete remission rate to 42%. The original paper incorrectly reported in the text refers to a complete remission rate comparable to that achieved with MOPP and many subsequent publications from this country during the past few years have confirmed that these drugs may be regarded as interchangeable in this context. The inadequate labelling of Fig. 1 on page 221 and the revised illustration on page 75 will presumably be corrected in future editions.

Although the presence of minor errors always tends to undermine the reader's confidence, in general this book is very readable, extremely informative and packed with innumerable references for those wishing to search for more detailed knowledge. It certainly deserves a place on the shelves of all reasonable medical libraries and in the personal collections of interested doctors who can still afford to purchase medical textbooks. A. M. Jelliffe.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

B.I.R. LIBRARY

The opening of the Institute's house for members to use the Library on Saturday mornings has been discontinued through lack of support. However, arrangements would be made for the Library to be opened between 10.00 a.m. and 1.00 p.m. on a Saturday if prior notice was given. Telephone 01–935 6237 or write to The General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

FUNCTIONAL LANDSCAPES IN THE BRAIN STUDIED WITH REGIONAL BLOOD FLOW MEASUREMENTS

The Mackenzie Davidson Memorial Lecture to be given by Dr. David Ingvar, University of Lund on May 19, 1977 at The British Institute of Radiology.

NEW HORIZONS IN INTENSIFYING SCREEN TECHNOLOGY

An all-day meeting organized by the Industry Committee of The British Institute of Radiology on May 20, 1977 at the Middlesex Hospital Medical School, London, W1. Registration details and information from the General Secretary, The British Institute of Radiology.

RECOVERY AND REPAIR

A work-in-progress meeting organized by the Radiology Committee of the British Institute of Radiology will be held at the Institute House on Friday May 20, 1977. Further information from the General Secretary, 32 Welbeck Street, London W1M 7PG.

EXPERIMENTAL AND CLINICAL APPLICATIONS OF KRYPTON 81M

An all-day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology to be held at the Hammersmith Hospital, London, W12 on June 3, 1977. Registration and details from the General Secretary.

PROGRESS IN EXPERIMENTAL RADIOTHERAPY

A meeting organized by the Netherlands Radiobiological Society in collaboration with the B.I.R. will be held on June 6–7, 1977 in Essex.

Subjects will include neutron radiobiology and radiotherapy, hypoxic cell sensitizers, chemotherapy and combined modalities.

Further details can be obtained from J. J. Broerse, Radiobiological Institute TNO, Lange Kleiweg 151 Rijswijk, The Netherlands, or S. B. Field, MRC Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12 0HS.

HYPOXIC CELL SENSITIZERS IN RADIOBIOLOGY AND RADIOTHERAPY

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

SIXTH INTERNATIONAL CONFERENCE ON THE USE OF COMPUTERS IN RADIATION THERAPY

Will be held at Gottingen on September 18–23, 1977. Further information from: R. E. Bentley, Physics Department, Royal Marsden Hospital, Downs Road, Sutton, Surrey, or Professor U. Rosenow, Strahlenabteilung, Unit.-Frauenklinik, D-34 Gottingen, Fed. Rep. Germany.

XIV INTERNATIONAL CONGRESS OF RADIOLOGY

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV International Congress of Radiology, Avenida Churchill 97—5th Floor, ZC 39, 20,000, Rio de Janeiro, Brazil.

TUMOUR ULTRASOUND '77

An international symposium on the science and clinical practice of ultrasound diagnosis and localization of tumours will be held in London, on December 5–6, 1977. This has been arranged in conjunction with the Annual Scientific Meeting of the British Medical Ultrasonics Group which will be held on December 7–8, 1977 at the same venue. A commercial and scientific exhibition will be held throughout both meetings. It is intended that the meeting will give a systematic coverage of the field and that the published proceedings will provide an up to date view of the subject. For registration and abstract forms or further details write to Dr. Ralph McCready, Department of Nuclear Medicine and Ultrasound, Royal Marsden Hospital, Downs Road, Sutton, Surrey, U.K.

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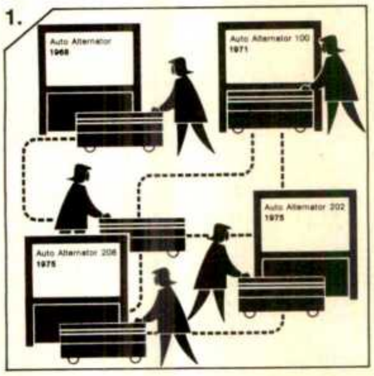

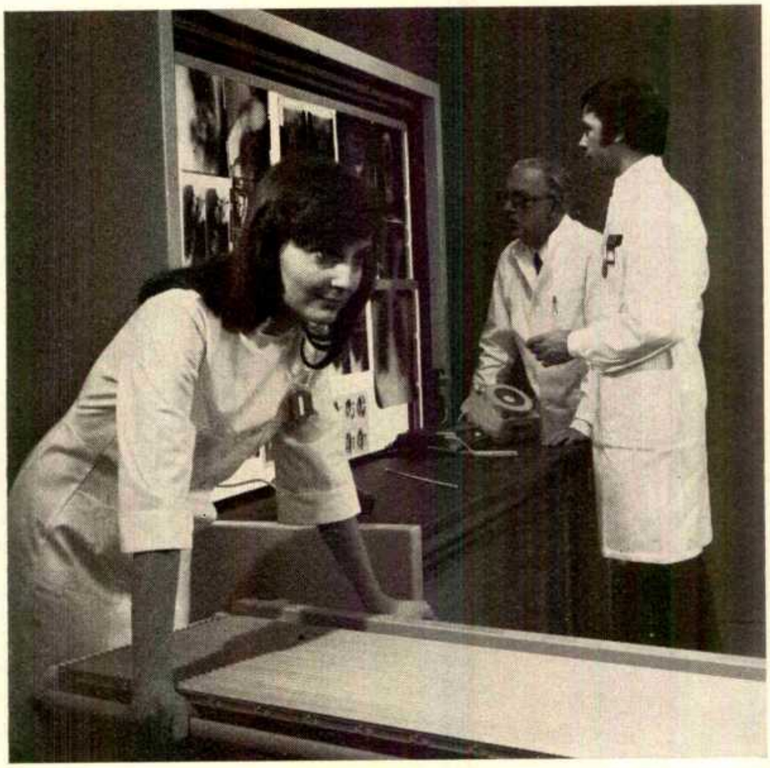

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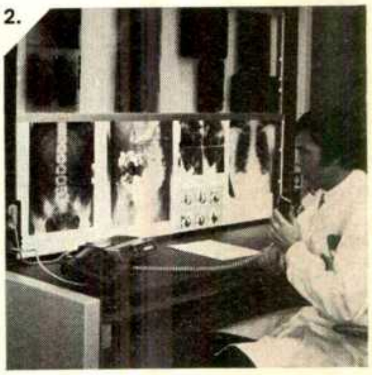

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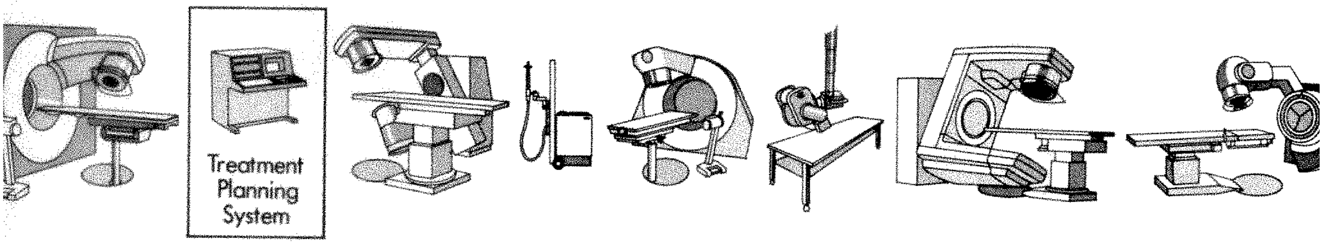

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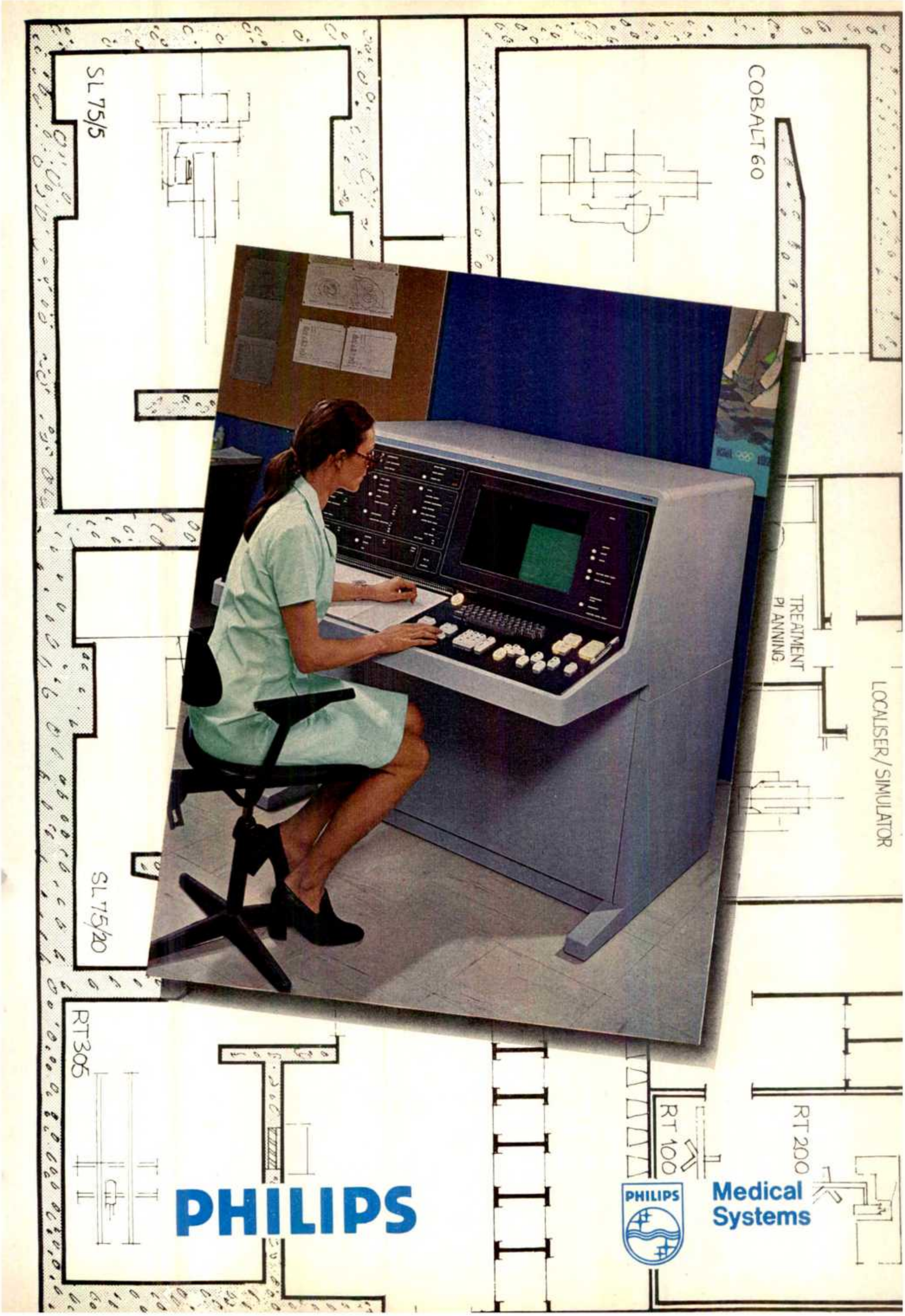

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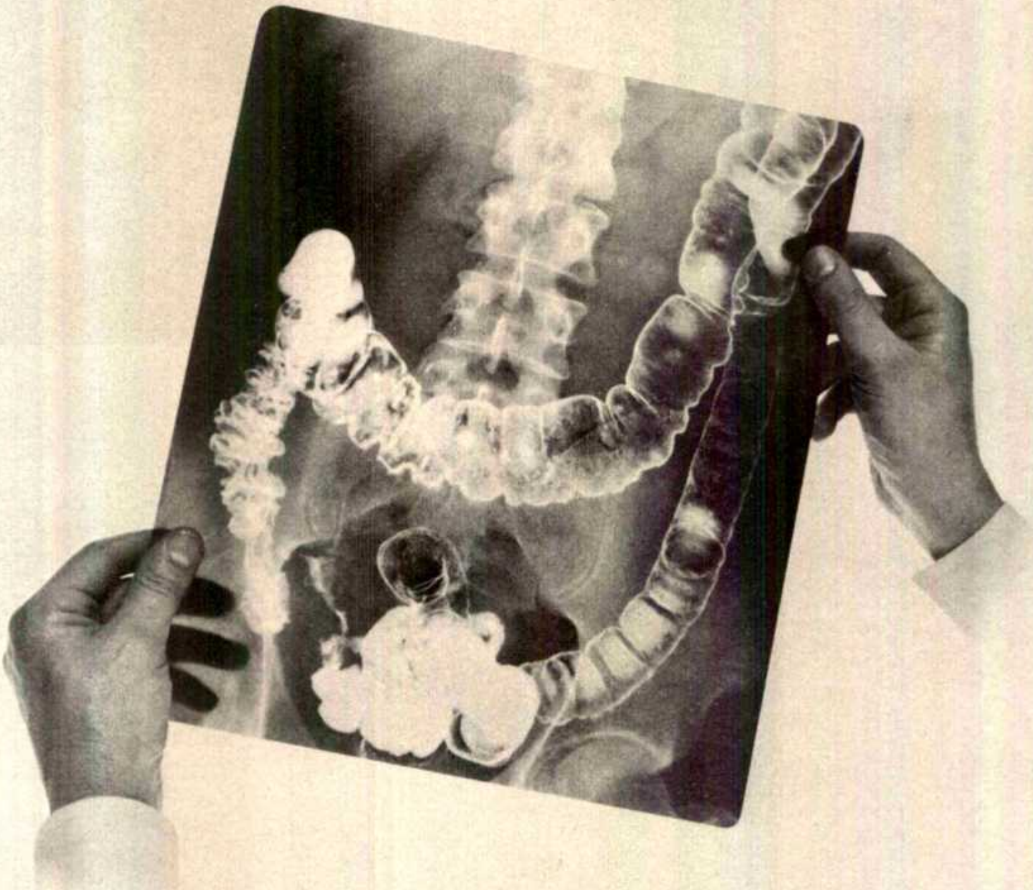

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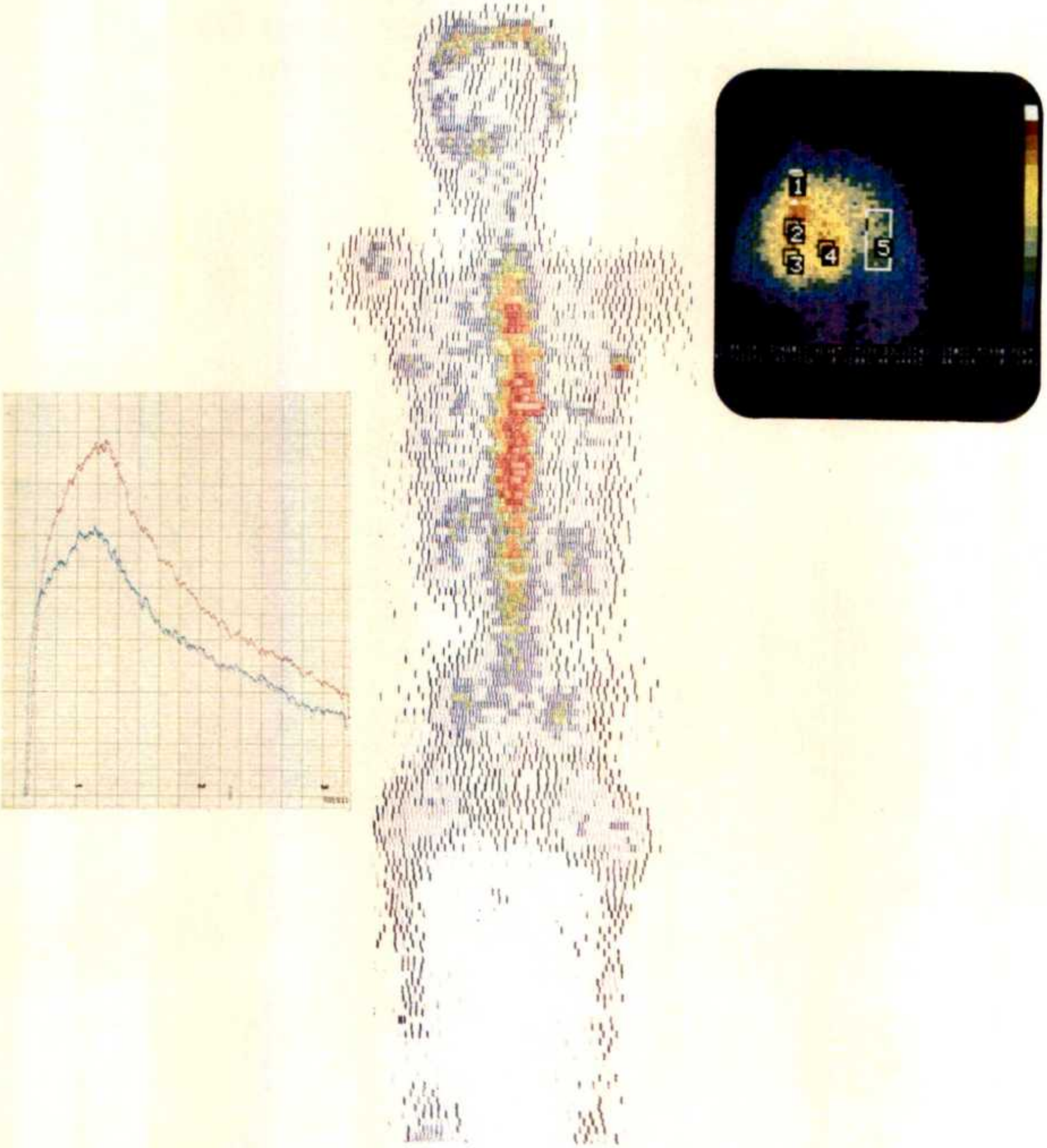
Overall evidence



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1

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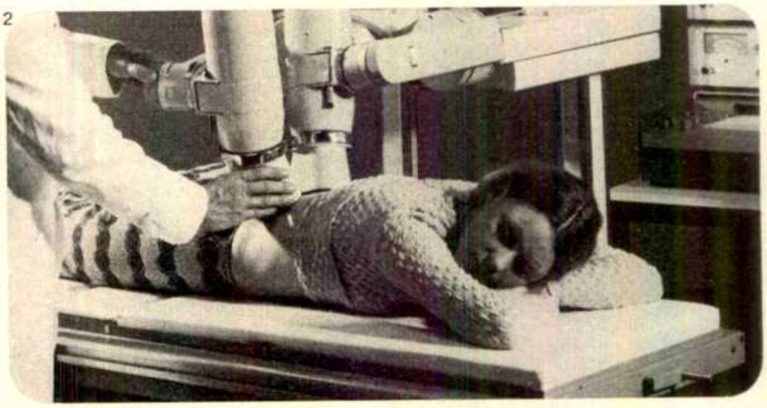

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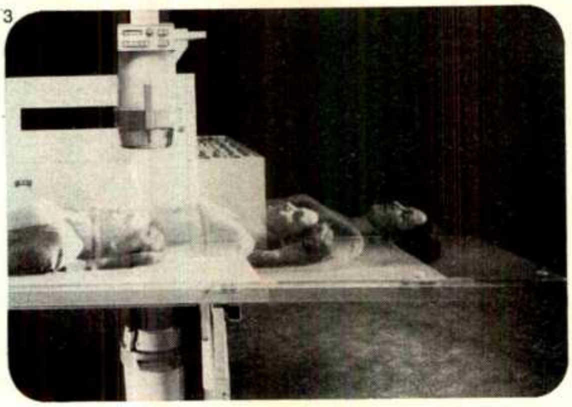

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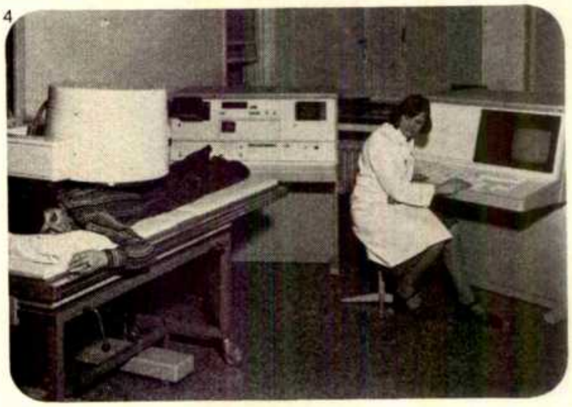

The range of equipment in Philips Nuclear Medicine Programme include a **Microcuriemeter** for rapid calibration of prepared radio-pharmaceuticals prior to patient administration, as well as **Automatic Sample Changers** (photo 1 shows the 100 sample version).

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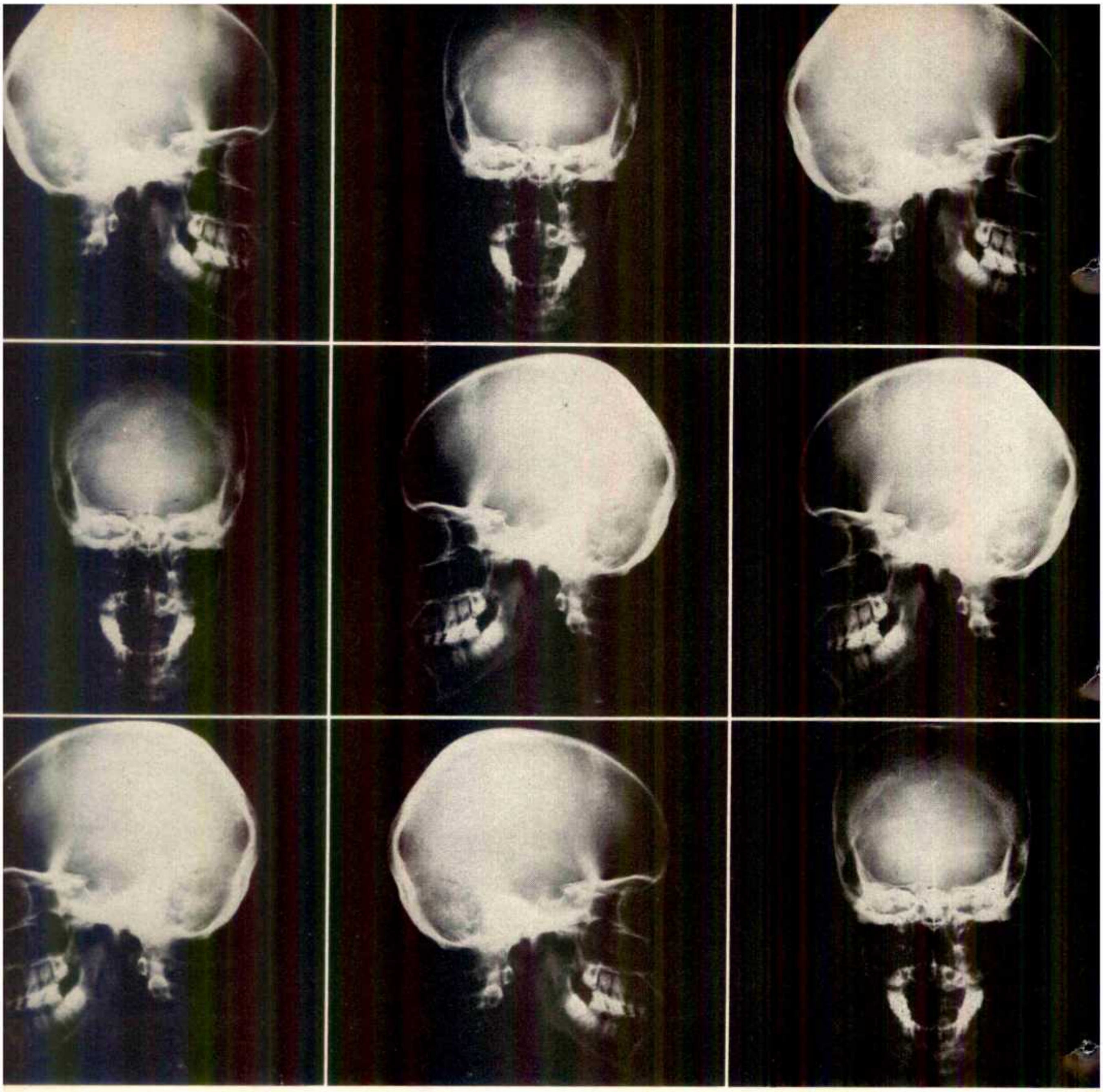

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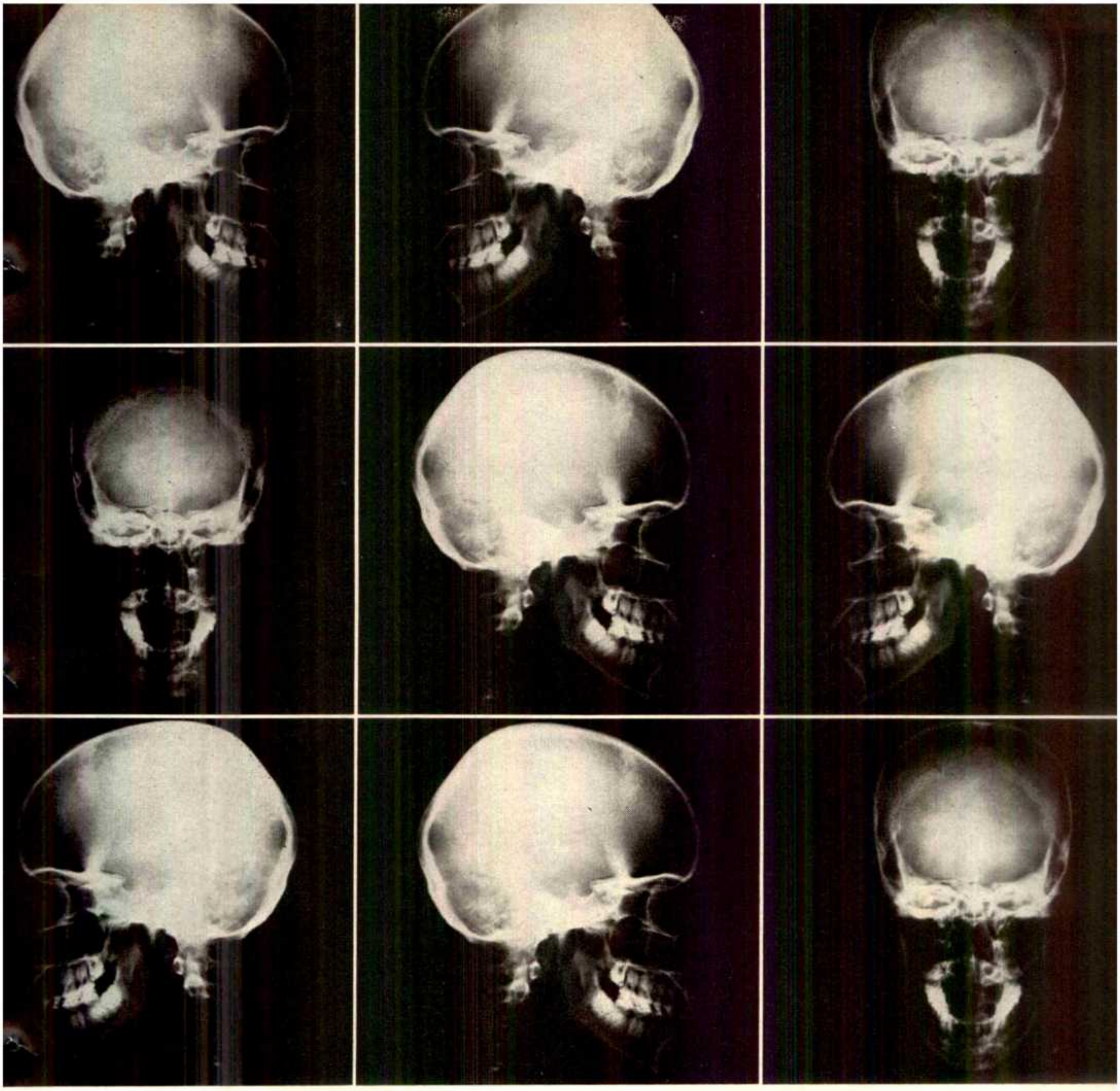

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Three-dimensional ultrasonic scanning – Principles and practical experience
S. Campbell and A. Roberts (Great Britain)
Fetal respiratory movement patterns in normal and abnormal pregnancy
I. Donald (Great Britain)
Scope and limitations of newer ultrasonic techniques
P. Fish (Great Britain)
Recent progress in the field of Doppler devices
M. Hansmann (FR Germany)
Recent advances in the assessment of fetal growth with follow-up studies
D.R. Hill and D.O. Cosgrove (Great Britain)
Ultrasound in cancer diagnosis: recent progress, present problems and future prospects
P. Jouppila (Finland)
Threatened abortion: A comparative study by ultrasonic, clinical, biochemical and histopathological methods
T. Kobayashi (Japan)
Grey scale echography in breast cancer
G. Kossoff (Australia)
Automated ultrasonic scanning techniques
A. Kratochwil (Austria)
Present results of grey scale ultrasonography in gynaecology
Ultrasonic diagnosis in orthopedic surgery
A. Kurjak (Yugoslavia)
The role of grey scale in the direct diagnosis of fetal malformations and abnormalities
G. Leopold (USA)
Grey scale echography in the field of retroperitoneum
S. Levi and J. Keuwez (Belgium)
Tissue characterization in vivo: semiautomatic method
H. Meire (Great Britain)
Pancreatic and liver ultrasonography – its potential and limitations
Y. Nimura (Japan)
Ultrasonocardiotomography
H. Takeuchi (Japan)
Grey scale ultrasonic diagnosis of ovarian carcinoma
D. N. White (Canada)
Colour coded differential ultrasonic Doppler scanning system for the carotid bifurcation and its clinical results on approximately 1000 cases

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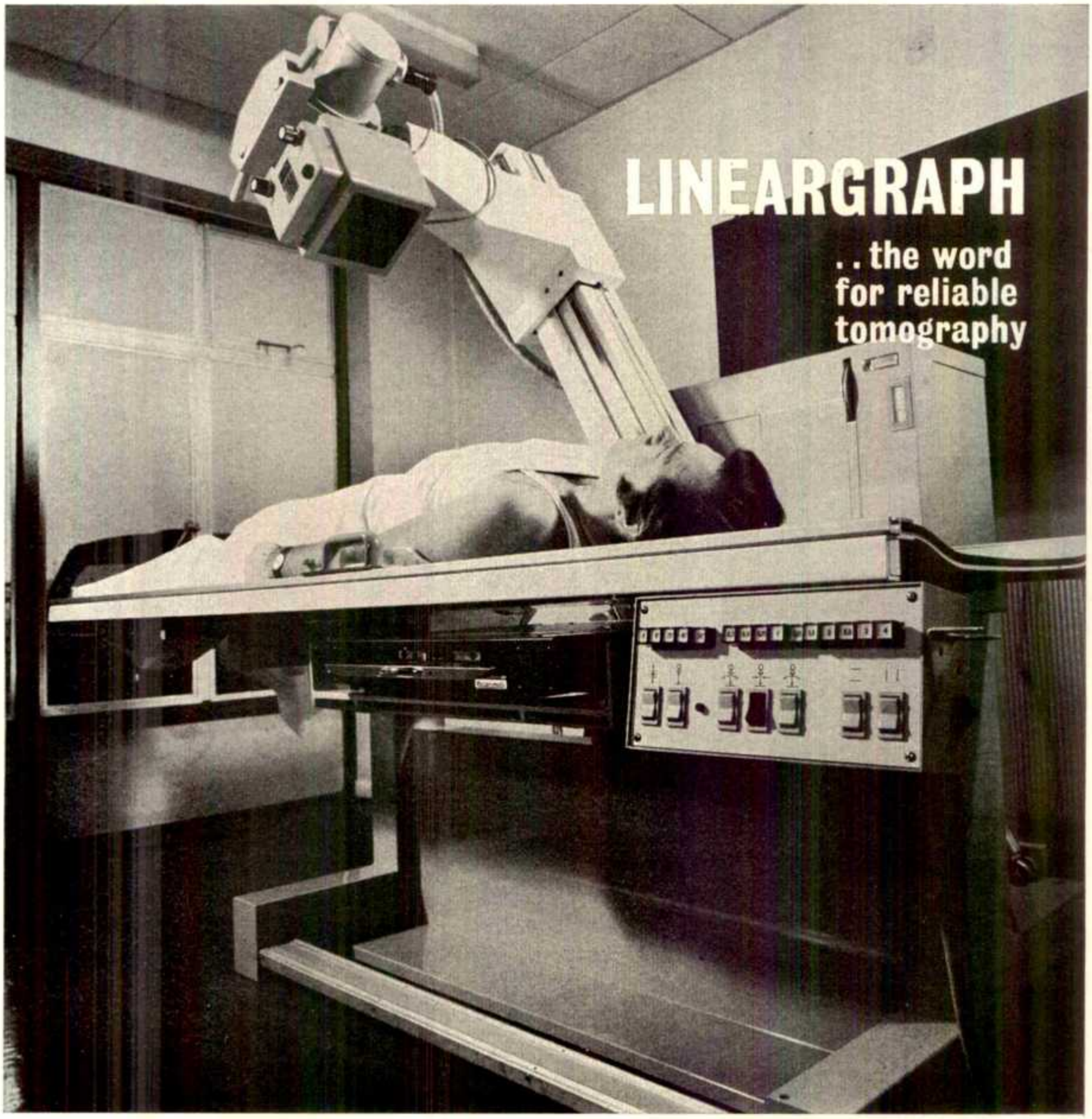

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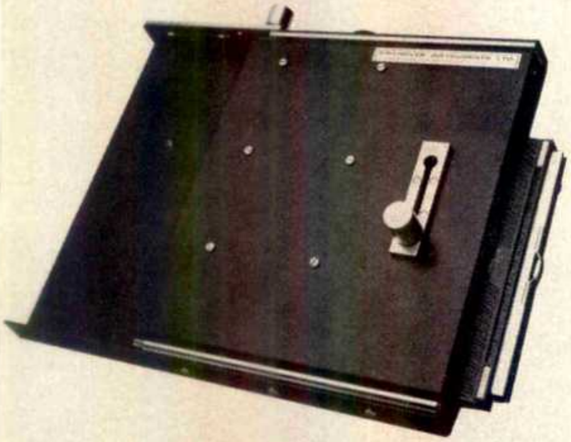

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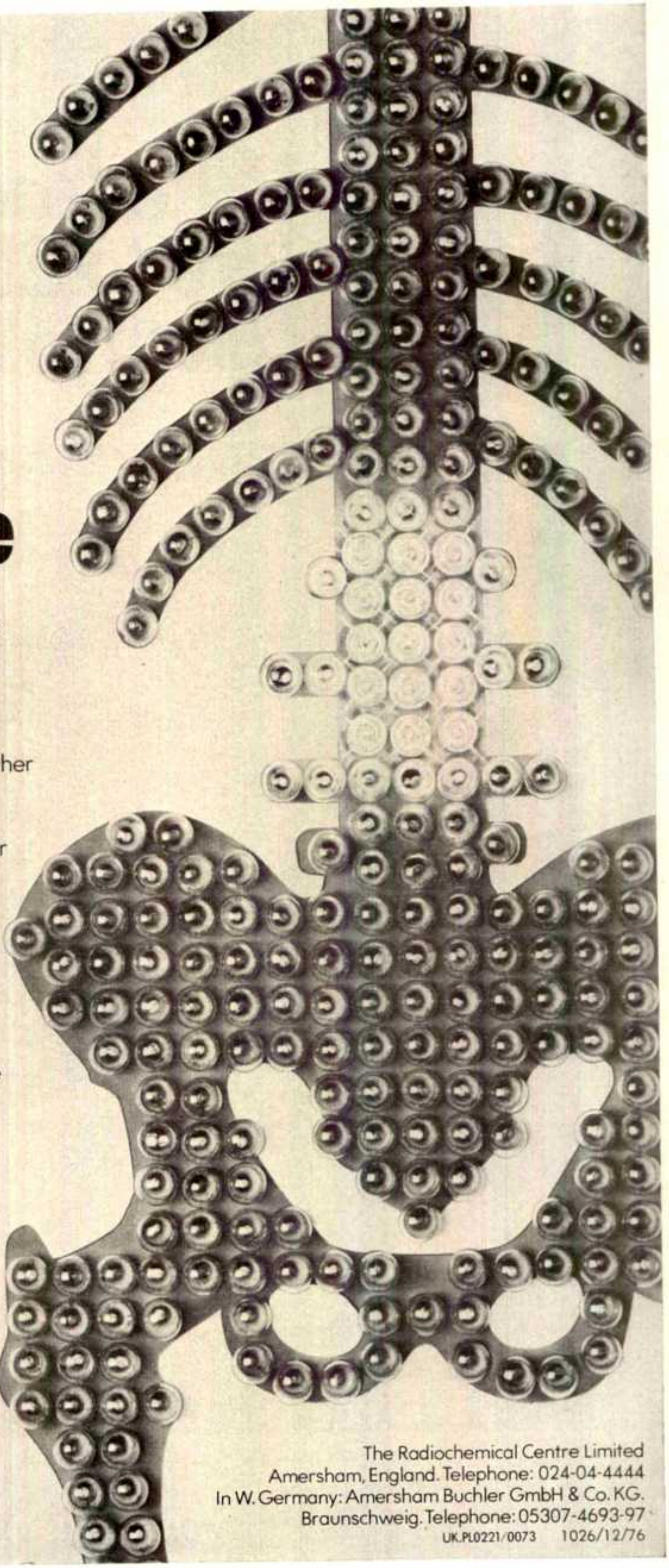

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(1) Subramanian *et al*, *J. Nuc. Medicine*, vol. 16, pp. 744-755, 1975.

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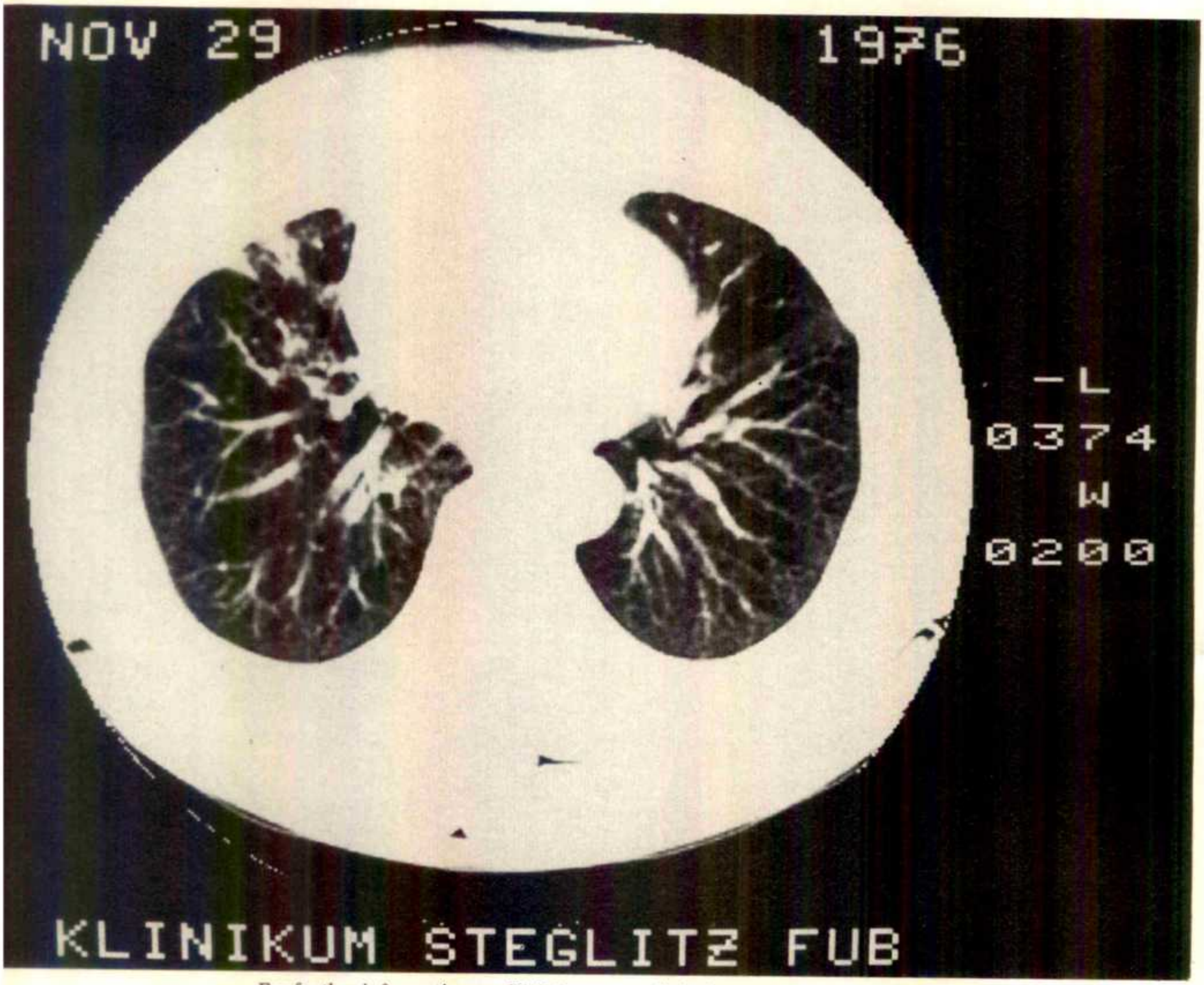

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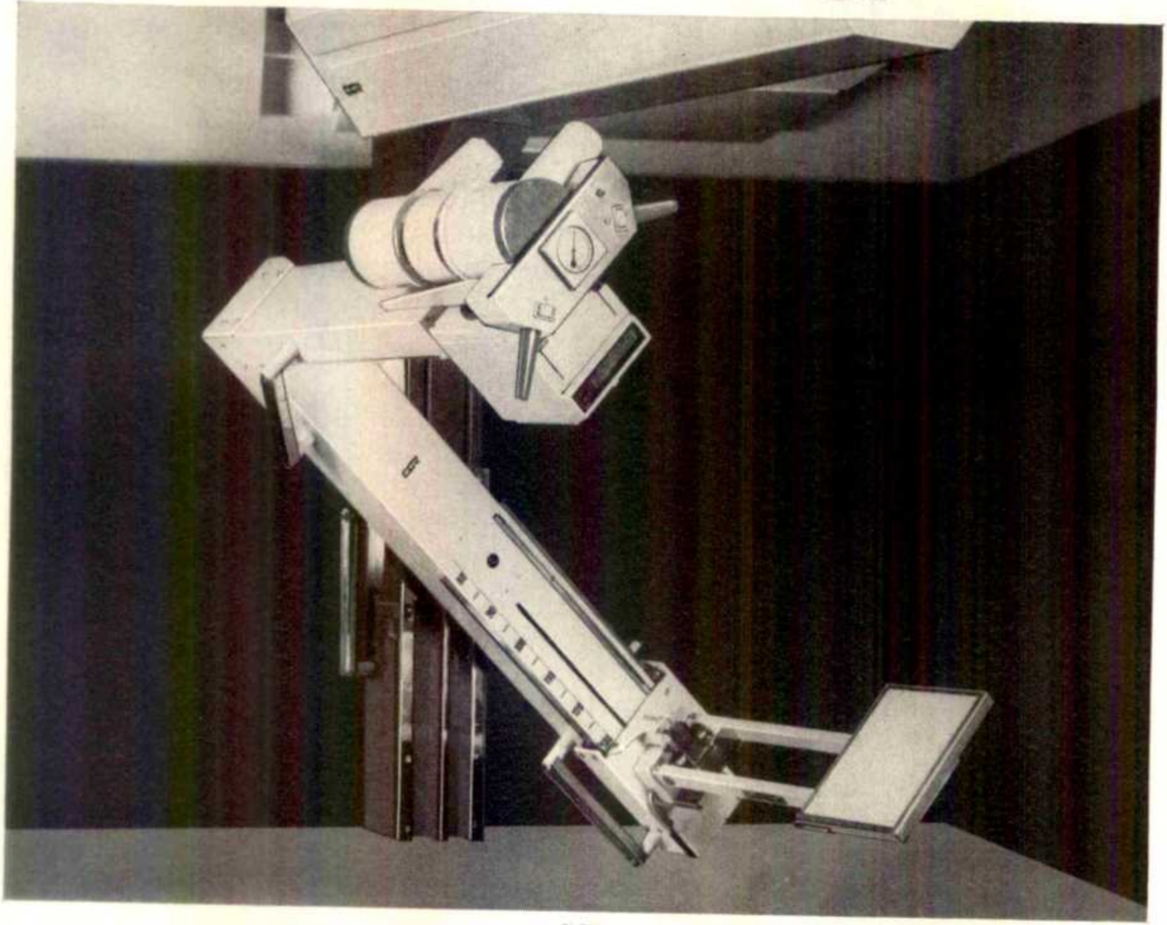

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Installations shown—(Above) Clinac 6X and (Center) Clinac 18, Central Arkansas Radiation Therapy Institute, Inc., Little Rock, AR; (Right) Clinac 4, Sequoia Hospital District, Radiation Oncology Dept., Redwood City CA

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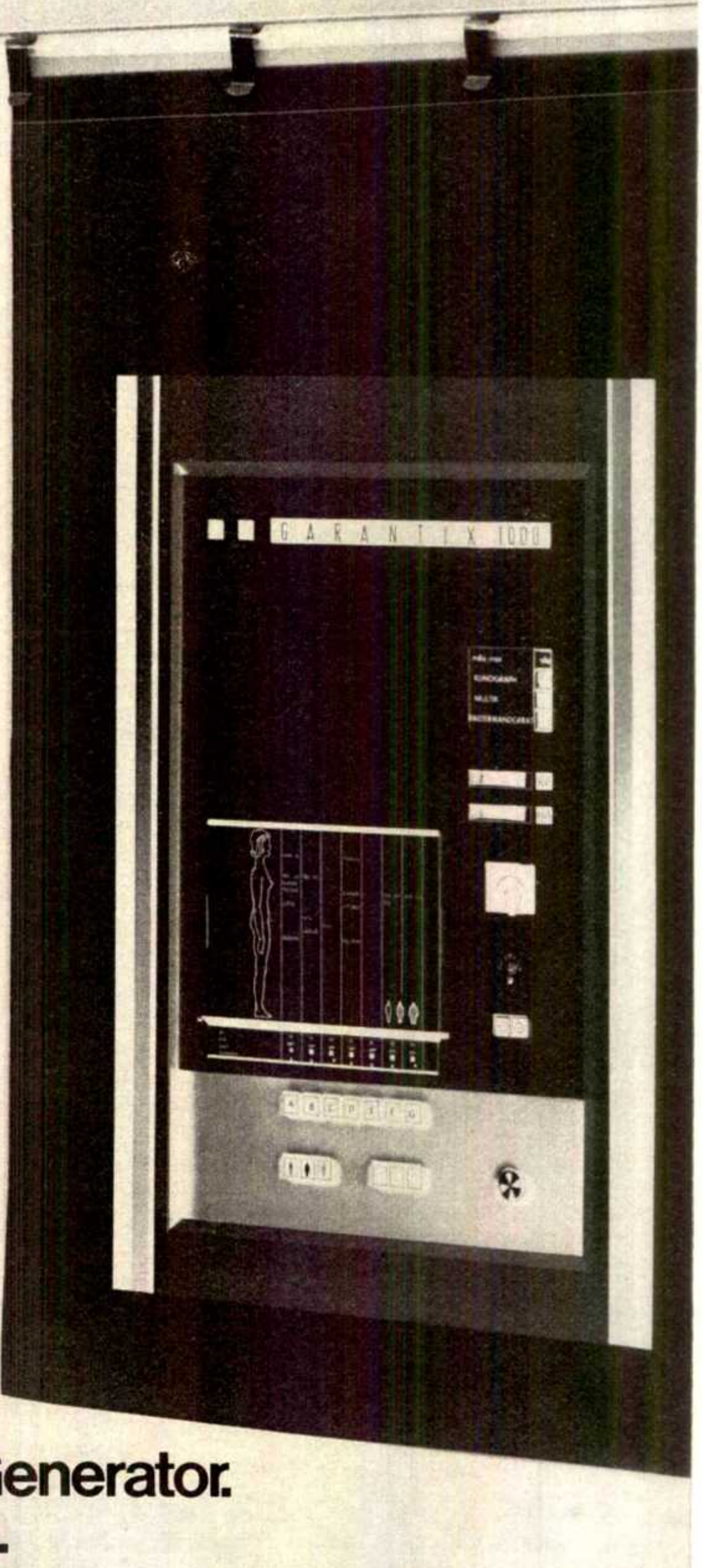

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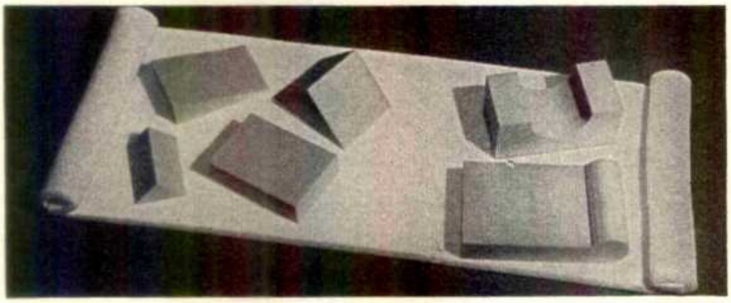

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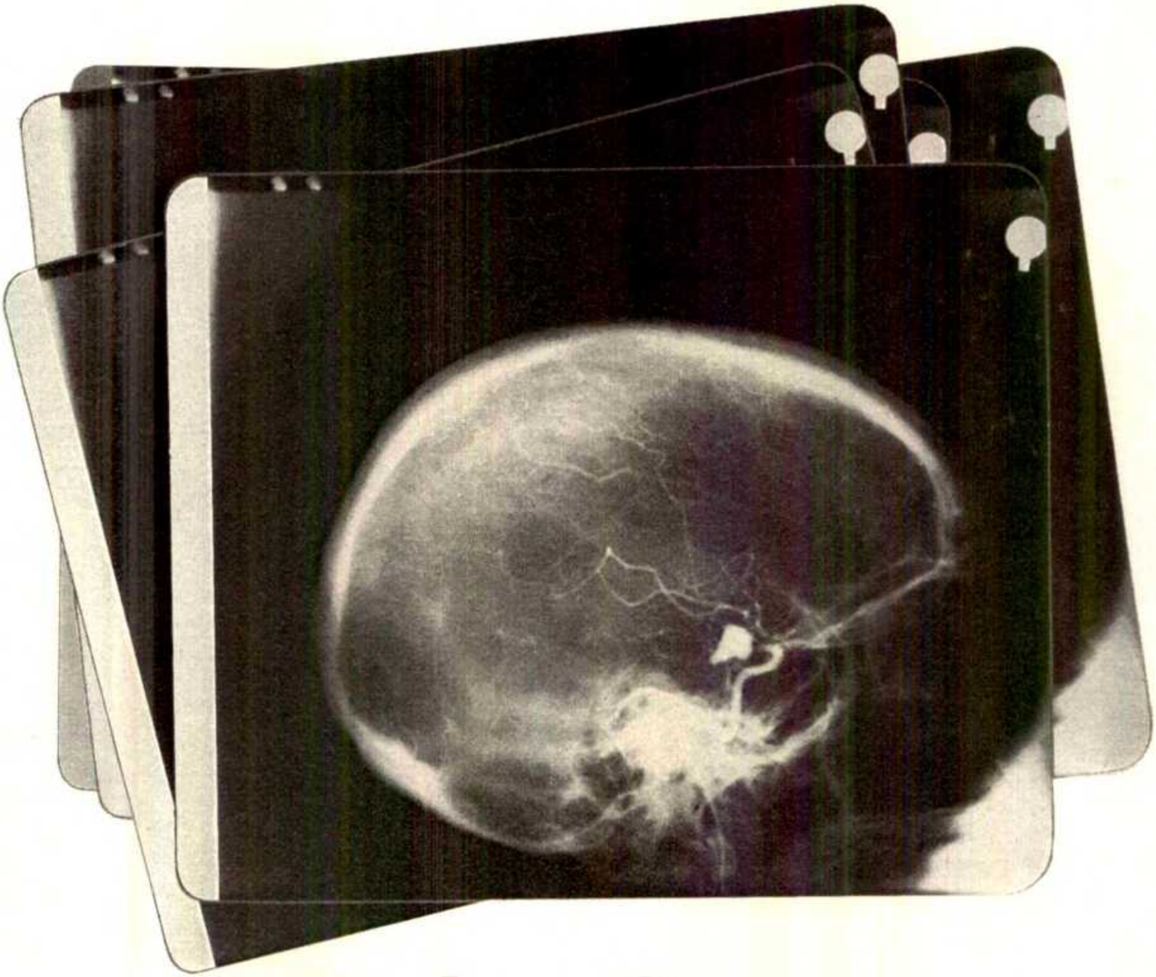

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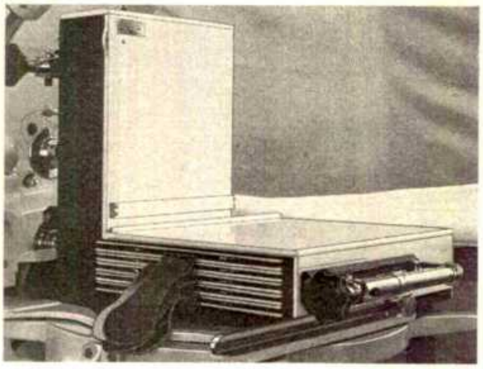

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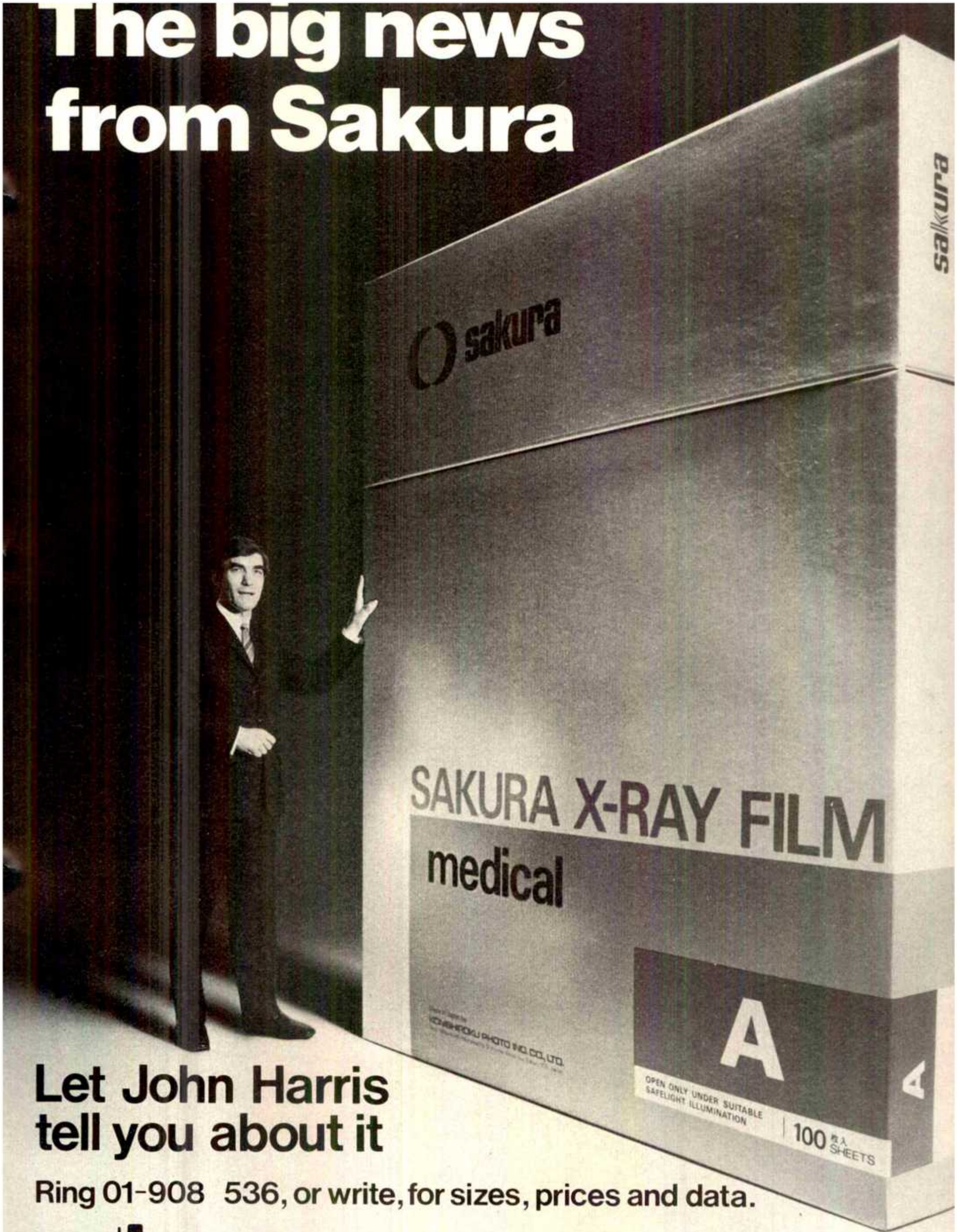
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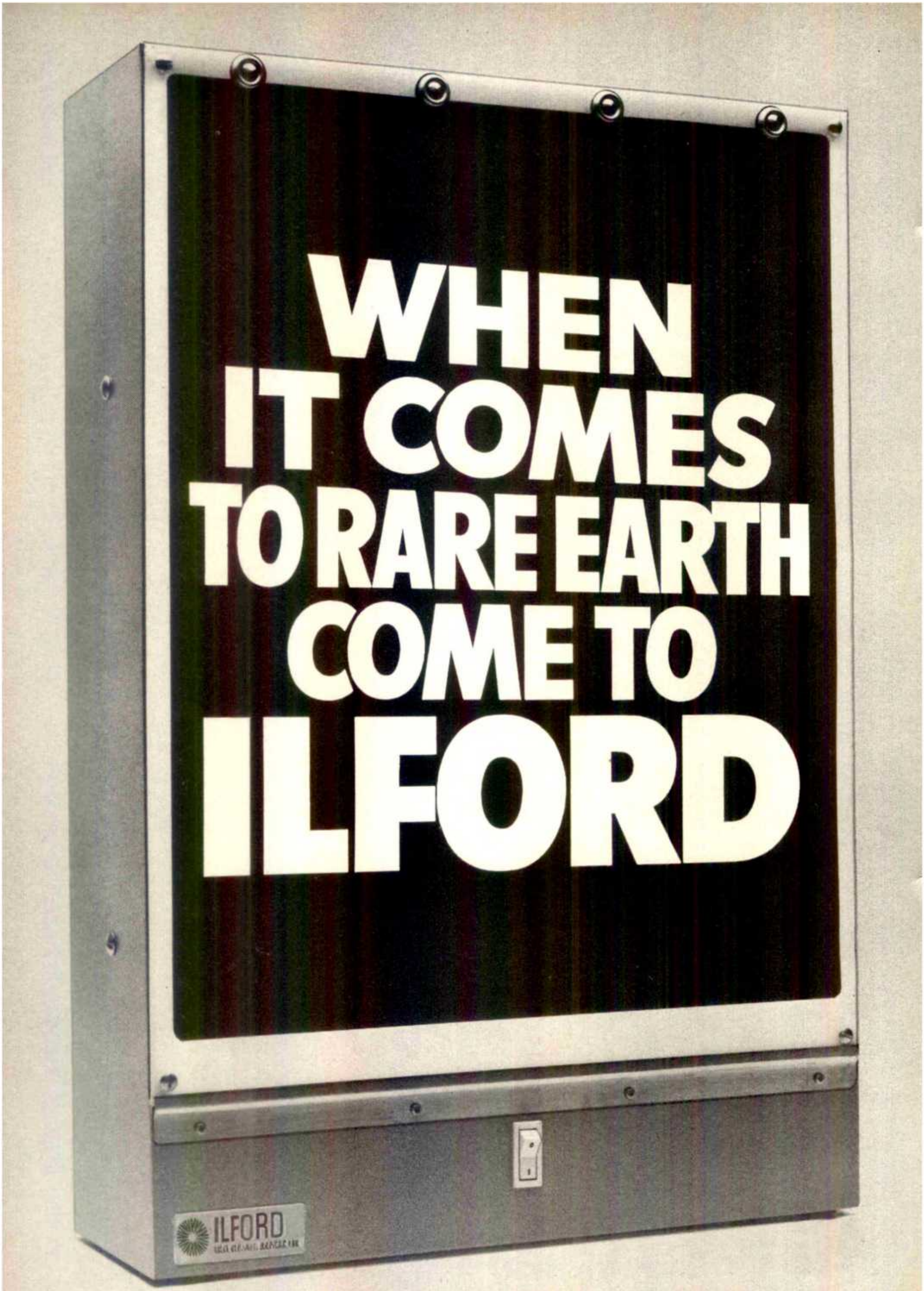
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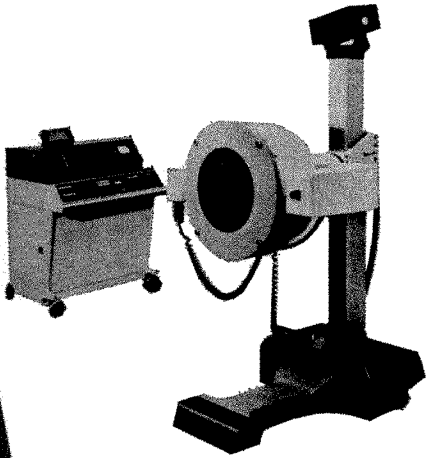

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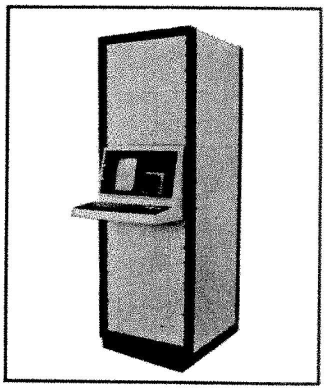

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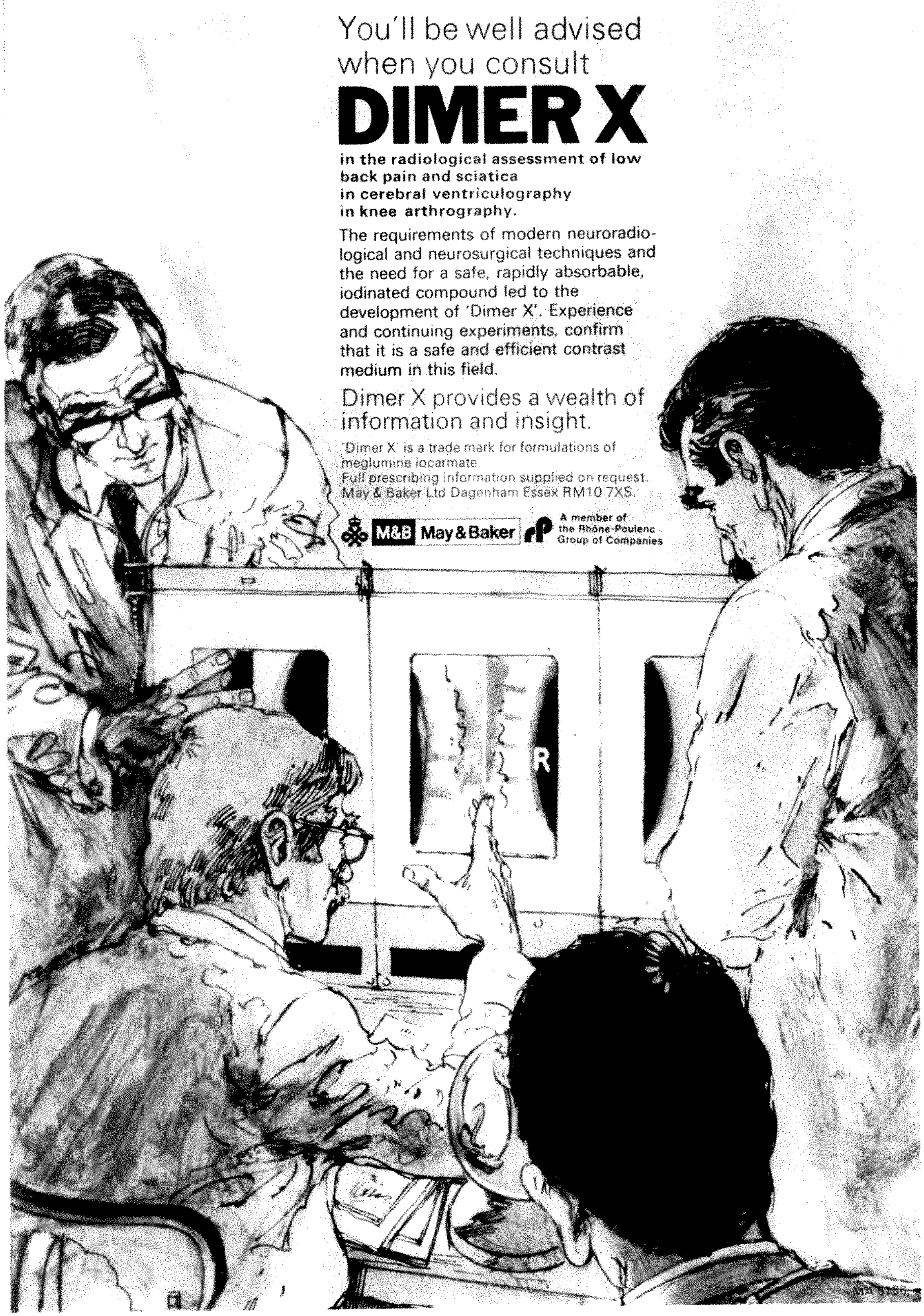

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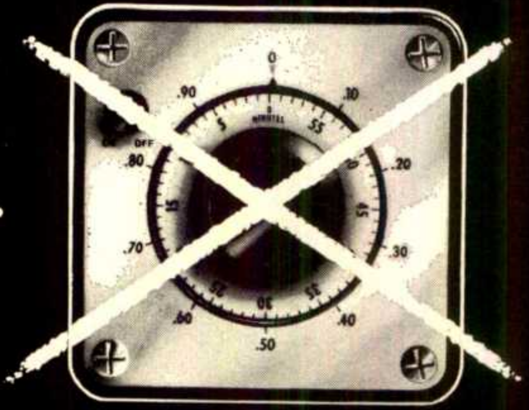

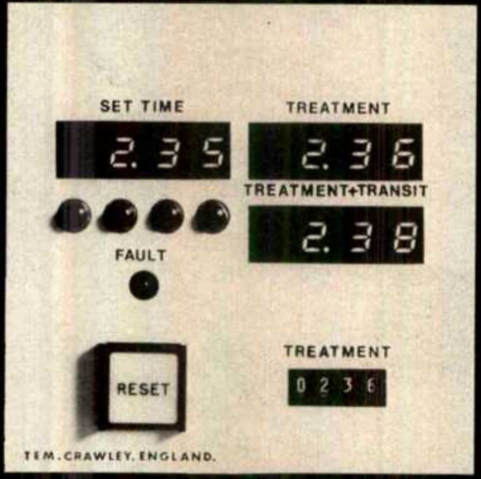

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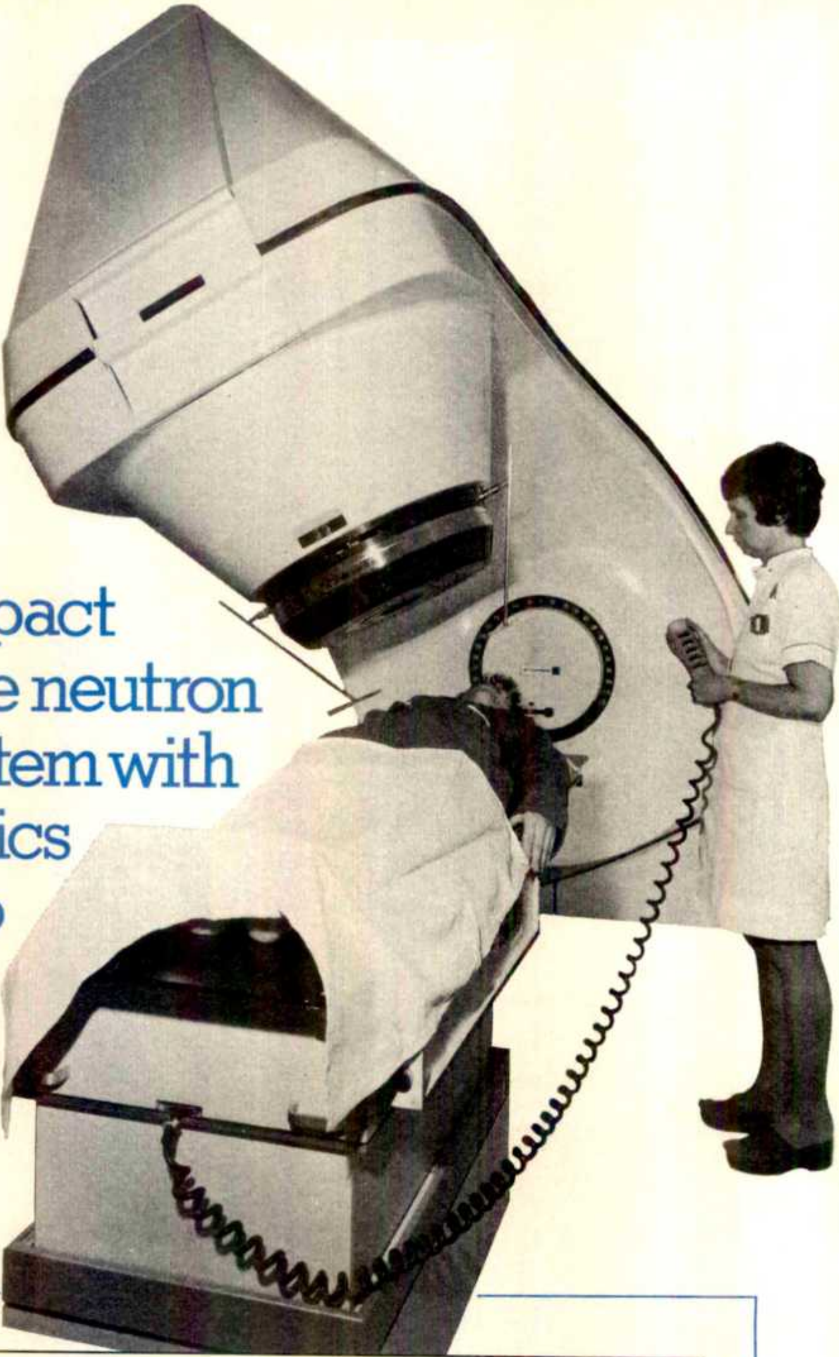

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PERFORMANCE DATA FOR THE NEW MODEL "CP" 42 SYSTEM (a)

	(42 MeV P on thick Be) No Filter	Filter (b)
Dose Rate in Air (Rad/Min) (c)		
Expected performance	127.0	71.0
Guaranteed performance	84.0	47.0
Depth for 1/2 dose at maximum (g/cm²) (c) (d)	12.6	14.7

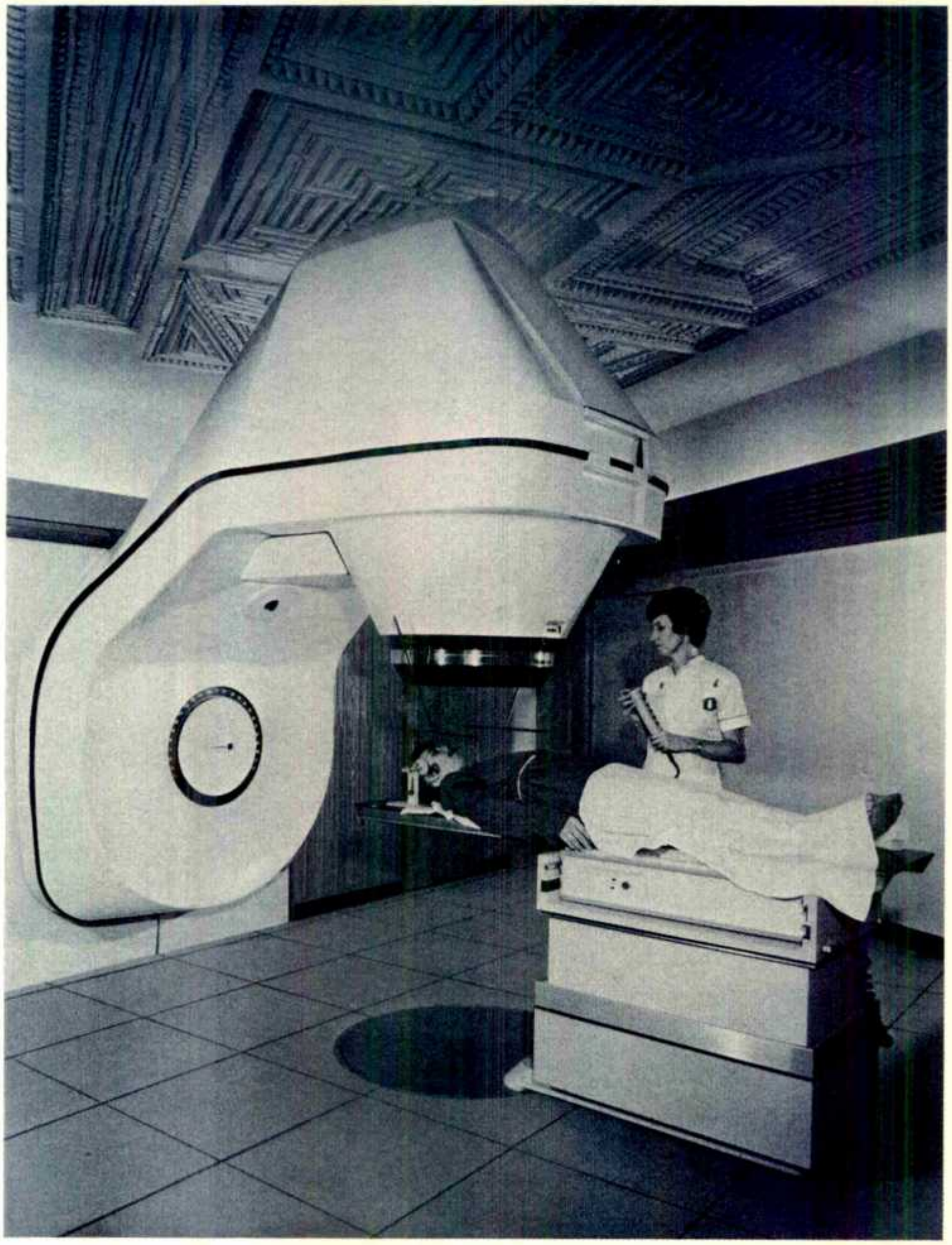
Notes:

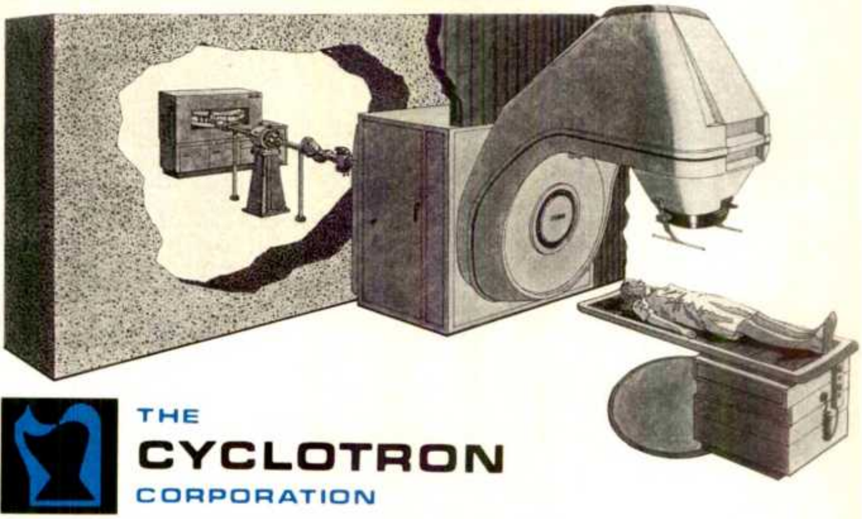
(a) For therapists willing to accept a lower depth for 1/2 dose and lower dose rate, the Model "CP" 30 is available.

(b) Filter is 6 cm. polyethylene.

(c) $n + \gamma$, 10 cm. X 10 cm. field at 125 cm. SSD.

(d) Depth for maximum dose (g/cm²), depth for 90% of maximum dose (g/cm²), entrance dose % of dose at maximum build-up, and gamma component in air were measured for 35 MeV protons on thick Be target. The results with and without filter respectively were as follows: 0.60 and 0.82; 0.2 and 0.2; 40.0 and 43.0; 8.9% and 13.5%.





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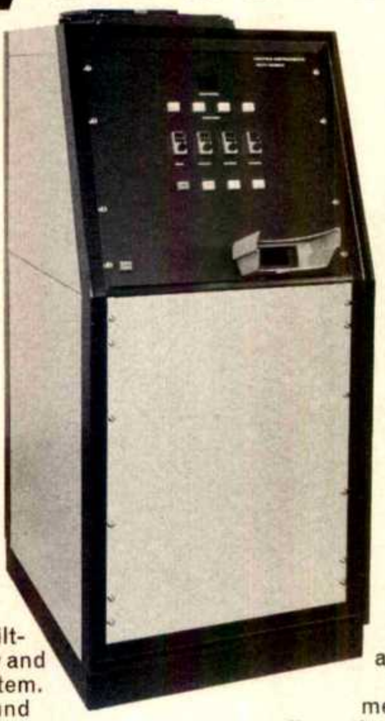

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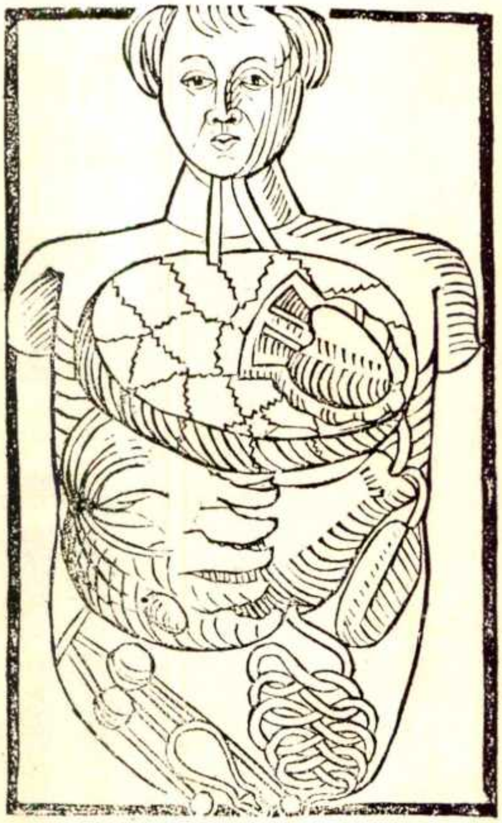

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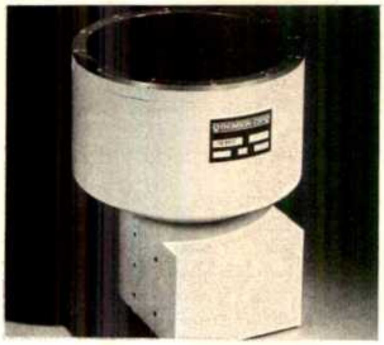

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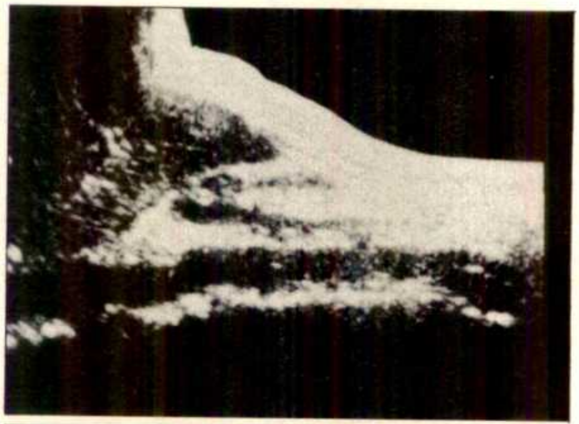

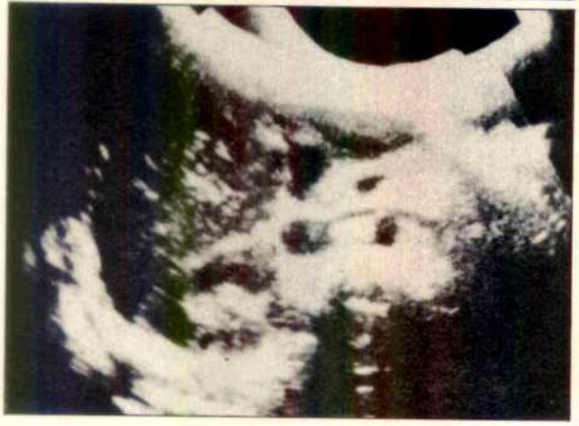

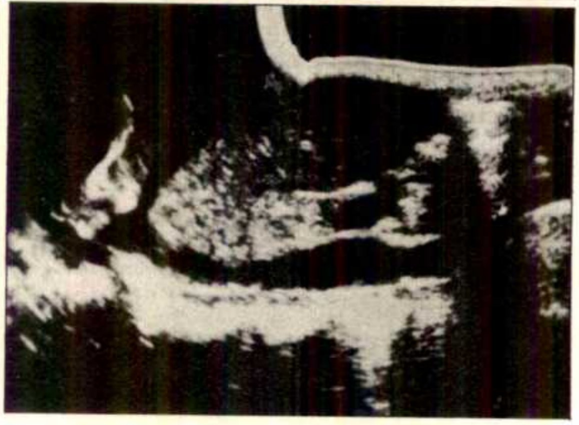

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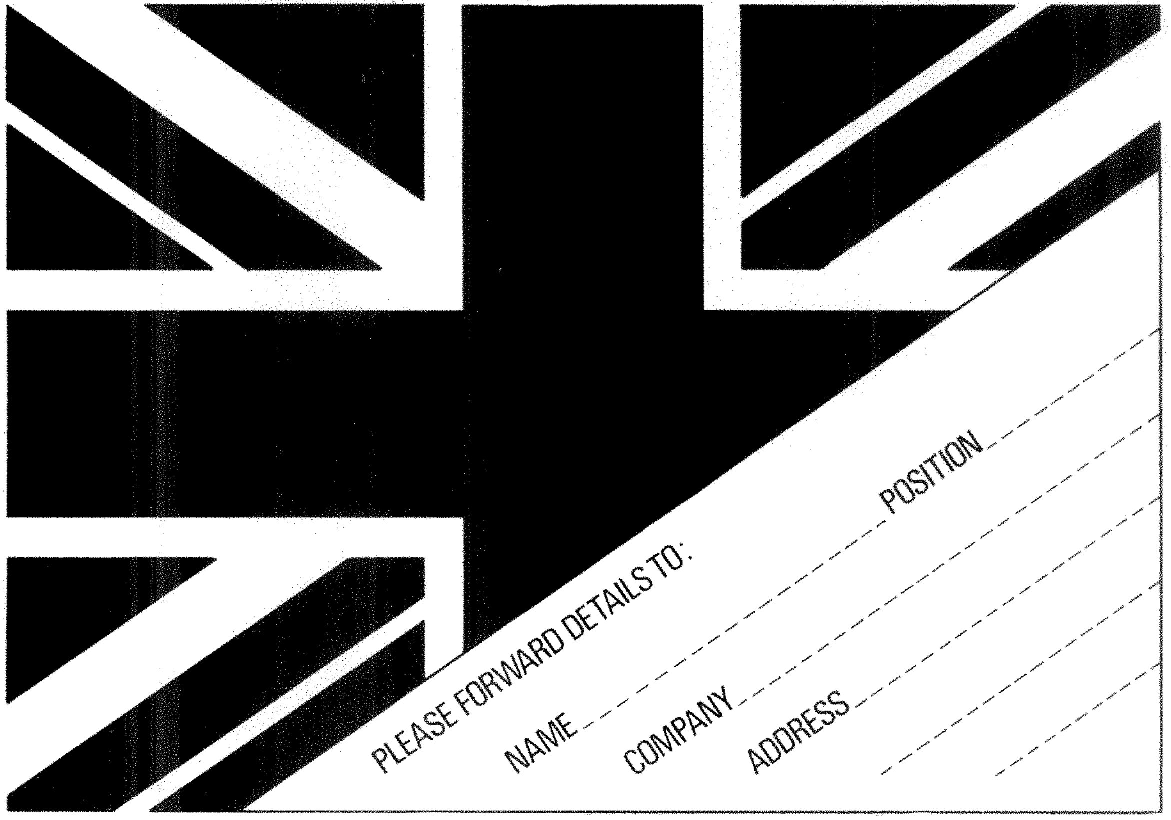

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1977, *British Journal of Radiology*, *50*, 379–380

VOLUME 50 NUMBER 594 JUNE 1977

The British Journal of Radiology

Radiology now

Ultrasound—current status and prospects*

The comparatively recent introduction of electronic storage of grey scale images on commercial ultrasound scanners has greatly increased their diagnostic potential beyond the confines of the pregnant uterus to include liver, pancreas and other organs. The proliferation of ultrasound scanners, both at home and abroad, has not been matched by an increase in teaching and training programmes, and consequently a significant proportion of scanners is being operated by untrained staff who cannot capitalize on the full potential of the equipment. It has also to be accepted that present scanners require a high degree of operator expertise to obtain satisfactory images, and a full medical knowledge of the anatomy and pathology of the area under investigation is essential if the maximum diagnostic information is to be obtained and incidental abnormalities detected and correctly interpreted. For historical reasons a surprising number of scanners are being operated by personnel who are not medically trained, and this must reduce the clinical value of the service they offer, quite apart from the medico-legal implications. How will the situation change in the near future? Firstly, current output of trained personnel must be increased and the involvement of a professional organization would probably help here. The recent introduction of a Diploma exam in Medical Ultrasound by The College of Radiographers is a significant step in the right direction. Secondly, we need scanners which are less operator dependent and therefore, presumably, more automatic. There are several signs as to how this may be achieved and the most evident is the advent of the so-called "real time" scanners. The term "real time" is borrowed from computer jargon and has no meaning whatever to ordinary mortals. I wonder why they aren't just called automatic scanners since their main value is that they free the operator from the skill and duty of manually sweeping the transducer over the area of interest, and from the mechanical constraints of a scanning frame. Their production of rapid sequential images "in real time" is their most impressive feature to the novice, but one of their least useful features in clinical practice. However, the currently available automatic scanners have markedly worse resolution than the present manually operated scanners, their field of view is limited, and their grey scale characteristics poor. Such scanners are, however, in their infancy, and the next year or two should see a significant improvement in their performance.

An alternative approach is that devised by Kossoff *et al.* (1975) namely a completely mechanically operated water bath scanner, which would appear to be ideally suited to operation by a technician with limited knowledge of the precise anatomy and pathology of the area under investigation. A series of routine "slices" will be taken and reported by a radiologist rather like radiographic tomograms. The early results from Kossoff's "Octoson" were most impressive and exciting but commercial exploitation of his brainchild has been depressingly tardy.

Part of the price one must pay for using such a machine, however, is the complete loss of the interaction between the operator and the imaging device. This interaction is vital when examining a structure such as the pancreas or fetal spine with conventional equipment, the operator steering the scanning frame into a plane in which the area of interest is optimally displayed, frequently a completely unpredictable inclined oblique plane. This facility will be enhanced when using the freely mobile hand held automatic scanners and this feature, together with the likely cost differential, will probably militate in favour of these devices. If this is so, the need for skilled and knowledgeable operators will persist and the need for more and better training will be increased.

For the meantime we must make the best of what we have in more conventional scanners, not least because they will doubtless be with us for many years and remain the mainstay of our diagnostic

---

* Reprints from: Dr. H. B. Meire, Department of Radiology, Northwick Park Hospital and Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ.

ultrasound service during that time. Much can still be achieved in improving their performance, and the recent introduction of the Searle "Pho Sonic" with its mini-computer and digital memory must rank as one of the more significant advances in this field during 1976.

A number of people have feared that the advent of computer assisted body tomography will pale ultrasound into obscurity. This seems unlikely to happen for many different reasons. Each technique measures a completely different physical property of tissues, and will thus often yield different information, and have different indications and limitations. Ultrasound has the benefit of being cheap and harmless, and must surely remain the first choice imaging technique in most cases of abdominal disease.

The early results from our department suggest that the potential diagnostic accuracy for both techniques is not greatly different for most abdominal organs. The value of ultrasound is, however, frequently limited due to interference from bowel gas, whilst the resolution of computed tomography images may be degraded by organ movement during the comparatively long scanning period.

It should also be remembered that enormous sums of money have been invested in research and development of computed tomography, and if similar sums were poured into ultrasound research and development the position might be rather different.

The efficient and economical use of a computerized tomographic scanner requires maximum patient throughput and this, coupled with the desire to reduce patient radiation exposure to a minimum, should dictate that the number of cuts per patient be kept to a minimum. If ultrasound scanning were used first to identify the level of the region of interest the C.T. examination could then be limited to this level, and we may therefore even find our ultrasound work load increased!

H. B. Meire

REFERENCE

Kossoff, G., Carpenter, D. E., Radovanovich, G., Robinson, D. E., Garrett, W. J., 1975. Octoson; a new rapid multi-transducer general purpose water-coupling echoscope. *Excerpta Medica, Congress Series, 363*, 90–95.

Book review

Diagnostic Neuroradiology (two volumes). By J. N. Taveras and E. H. Wood, 2nd edn., 1976 (Baltimore, Williams and Wilkins), £47·50.

The first edition of this major textbook appeared in 1964 and won rapid acclaim as the outstanding work in this field. The long-awaited second edition is now published and has grown to two volumes.

Volume I consists of 500 pages with 500 illustrations. The normal and abnormal skull are discussed in the first 230 pages and pneumography in the remaining 300. Volume II contains some 700 pages and 580 illustrations. It consists of five parts, cerebral angiography, selection of diagnostic procedure, inflammatory lesions of the C.N.S., head injuries, and diseases of the spinal cord. The new technique of computerized axial tomography introduced by EMI in 1972 is considered in the part dealing with selection of diagnostic procedure.

Neuroradiology has made remarkable advances in the last ten years, the most spectacular being the introduction of EMI scanning. This brilliant new technique has revolutionized the practice of neuroradiology and is undoubtedly now the primary investigation of choice in most cases with suspected intracranial lesions. The reviewer has the impression that the rewriting of the new edition was overtaken by the impact of the new method. Otherwise, it is difficult to understand how only 23 pages are devoted to it, whilst pneumography, a technique which is being largely supplanted by C.A.T. still occupies 300 pages. I would also have preferred more space in this major reference text for isotope scanning which is dismissed in two pages, the reader being referred to specialist texts. It is true that isotope scanning is also in most neurosurgical centres being replaced by C.A.T. scanning, but it merits fuller discussion in a textbook of neuroradiology, since neuroradiologists are now often responsible for brain scanning. These, however, are minor criticisms of a book which remains an outstanding reference text, the section on angiography being particularly comprehensive and valuable. As in the first edition, the book is printed on good quality art paper and the illustrations are generally of first class quality. The extensive references occupy 28 pages and are reproduced in both volumes, as is a 22-page index.

The authors are to be congratulated on producing such a monumental reference text. It is extremely sad that the publication of the new edition is overshadowed by the untimely death of Dr. Wood at the early age of 61.

D. Sutton.

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Changing patterns in malignant disease and its treatment

Presidential Address delivered at The British Institute of Radiology on May 15, 1975

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The treatment of malignant disease by X rays was first recorded at The London Hospital on August 10, 1903. The first X ray case book, as it was called, of the X-ray and Electrical Department, records on its first page the treatment of Elizabeth Sidgewick of Bow, a widow aged 55 who had a left mastectomy performed by Sir Victor Horsley in Saint Bartholomew's Hospital six years previously. Her records state that she was referred from the National Hospital for the Paralysed. She was complaining of pain down the right leg, extending from the groin to the knee, due to bone involvement by cancer and that glands were also involved. X ray treatment was started. Over three years' later the annotation written clearly in the legible handwriting of the period states that she was "still going strong, apart from lameness". A most remarkable and encouraging result for palliative radiotherapy. Glaring omissions from this early account of treatment are a complete lack of information with reference to dose, treated area, overall time, kilovoltage or filtration. Later records would suggest that the total dose was unlikely to have exceeded 2000 R and the overall time two weeks.

The first physical measurements of X rays were undertaken by Dorn in 1897 (Lorenz, 1930) who used a thermocouple for direct energy determinations, and in 1902 Holzknecht described a measuring device or chromoradiometer based on the photochemical effect of X rays on a mixture of KCl and Na_2CO_3. Many units were used during the next 30 years, including the Sabouraud-Noire (S-N) pastille, the photographic blackening unit of Kienbock and the ionization unit of Friedrich, but the standby of the radiotherapist was the unit skin dose or skin erythema dose (Pohle, 1927) which varied from 400 R for superficial X rays to 550 R for deep X rays.

As late as 1921 there were conflicting opinions on the value of X-ray therapy, and certain members of the medical staff of St. Bartholomew's Hospital visited Erlangen to evaluate the claims which were being made for the use of deep X-ray therapy in the treatment of cancer. The report of this investigation was published (Levitt, 1930) and dosage at this time and even much later was recorded in unit skin doses. In this investigation it was intended to treat two large series of cases: (1) by a single dose technique and (2) by a fractionated dose technique, but in an early review of the results of treatment, especially in the case of cancers of the upper air passages and also of the uterus, there was a striking superiority of the technique of fractionation. Many of the problems which confronted Levitt 45 years ago, such as the optimum fractionation method, are still with us and have not been resolved.

The dosage problem improved with the definition of the röntgen in 1928 and following the publication of "A dosage system for gamma-ray therapy" (Paterson and Parker, 1934). Later papers on interstitial radium therapy and a dosage system for cancer of the cervix (Tod and Meredith, 1938) were most distinguished and valuable contributions. By the late 1930s radium therapy was on a firm basis and it seemed that most cases of cancer which were cured were those treated with radium, and that X-ray therapy was mainly palliative. The armamentarium of the radiotherapist was restricted to radium needles and tubes, radon seeds and X rays. There were by now two main schools of thought in radiotherapy—those who followed an earlier and clinical approach when dosage was ill defined and who believed in the control rather than the cure of cancer, and those who were influenced by Ralston Paterson and the Manchester School and thought and talked about the cure of cancer. This was at the time a revolutionary concept, but it was beginning to be substantiated by follow-up figures.

The first attempt to introduce a scheme for recording the treatment of cancer on a national scale was made by the Radium Commission which, from 1929 until the National Health Service Act of 1948, controlled the supply of radium to radiotherapy centres. Some hospitals prior to 1929 had their own supplies of radium, but they were few in number and the National Radium Commission was established to remedy this situation. In 1939 the Cancer Act was passed and it required every county and county borough to provide adequate facilities for the diagnosis and treatment of cancer cases in their area. When the National Health Service Act came into force in July 1948 the Cancer Act was repealed and cancer records became the business of Regional Hospital Boards and Boards of Governors. Since 1929, therefore, records are available for most large radiotherapy centres of the response to treatment of malignant tumours in various sites.

In 1950, in his opening address to the VIth International Congress of Radiology held in London, Dr. Ralston Paterson stated that 25 years previously cancer of the buccal cavity was regarded as one of the most difficult and recalcitrant sites, and that now it was known to be one of the favourable sites with a reasonably good prognosis.

The medical student of 40 years ago saw many advanced skin cancers and rodent ulcers which had either been diagnosed late or no treatment had been prescribed because of a belief in an inevitably fatal prognosis. This same fatalism exists today even if less markedly than formerly, for there are still distinguished surgeons who express the opinion that the treatment of cancer is an overdose of morphine. For the last 50 years the radiotherapist has kept alive a continuous interest in the diagnosis, management and treatment of malignant disease. During this time the surgeons have shown less interest despite the surgical triumphs in the treatment of cancer of the breast, cancer of the colon and rectum, and cancer of the uterus. Surgical interest is tinged with pessimism and, until recently, the interest of physicians was minimal as they had no pill to cure cancer.

Techniques and Results of Treatment

Skin cancer

Malignant disease of the skin, excluding rodent ulcers and malignant melanomata, has a five-year survival rate of 87% (males) and 83% (females) (Registrar General 1966–67). It is important, therefore, to design techniques which will effectively sterilize the lesion and reduce to a minimum the dose to normal tissue. Usually this can be achieved by a judicious choice of the various methods available; contact X rays, superficial X rays, deep X rays, superficial applicators with an increasing availability of radioactive sealed sources such as iridium, caesium, radium, etc. An interesting example of the use of artificial radioactive isotopes is illustrated by the treatment of a very extensive superficial rodent ulcer involving the nose and adjacent cheeks of an elderly patient. The area presented sudden changes of curvature difficult to irradiate with superficial X rays without giving a high dose to the mucous membrane of the nose, and the risk of a dry nose and possibly an atrophic rhinitis. A typical γ-ray applicator would be hazardous and might cause a radiation cataract. This problem was solved by using a ^{32}P β-ray applicator. A plaster of Paris cast was first made of the nose and cheeks and an appropriate lead mask prepared. A chemical mixture of non-radioactive phosphorus and polythene was fashioned to fit the area to be treated and a second smaller lead mask to cover the applicator. The applicator was activated by irradiation at Harwell and returned as a radioactive ^{32}P β-ray applicator. The output was measured and two applications at weekly intervals given to a total dose of 2500 R. The accurately defined erythema around the lesion is seen in Fig. 1A and the final response to treatment in Fig. 1B. This is a simple example of the influence of new methods on the treatment of malignant disease of the skin. Skin cancer can be satisfactorily eradicated either by surgery or by radiotherapy. Surgery is indicated where a risk of radiation damage to normal structures is greater than the risk due to surgery. In cases where surgical treatment in order to be effective carries with it an inevitable consequence of mutilation, radiotherapy is usually the treatment of choice. For example, some patients with an invasive squamous carcinoma of the dorsum of the hand can be expected to respond to radiation as shown in Fig. 2A and 2B but care has to be taken in selecting the optimum method. Cancer of the lip in most cases responds favourable to radiotherapy.

A satisfactory result from treatment of cancer of the pinna can be expected in the absence of involvement of cartilage. Invasion of the perichondrium with accompanying pain and tenderness is an indication for surgery. Where radiotherapy is indicated a surface mould is usually the treatment of choice and the availability of iridium makes this method easier and simpler to use than the radium needles and tubes of earlier decades.

Tumours in the mouth

With the reduced incidence of buccal cancer in the last 30 years there has grown up a tendency for cancer of the tongue to be treated initially by surgery. This must be regarded as a retrograde step. Even in the hands of masters of surgical technique the response of primary tongue cancer was of the order of 15%, whereas most radiotherapists can achieve local sterilization of the anterior two thirds of the tongue in 80% to 90% of cases. Failures may later be cured by salvage surgery whereas the failed

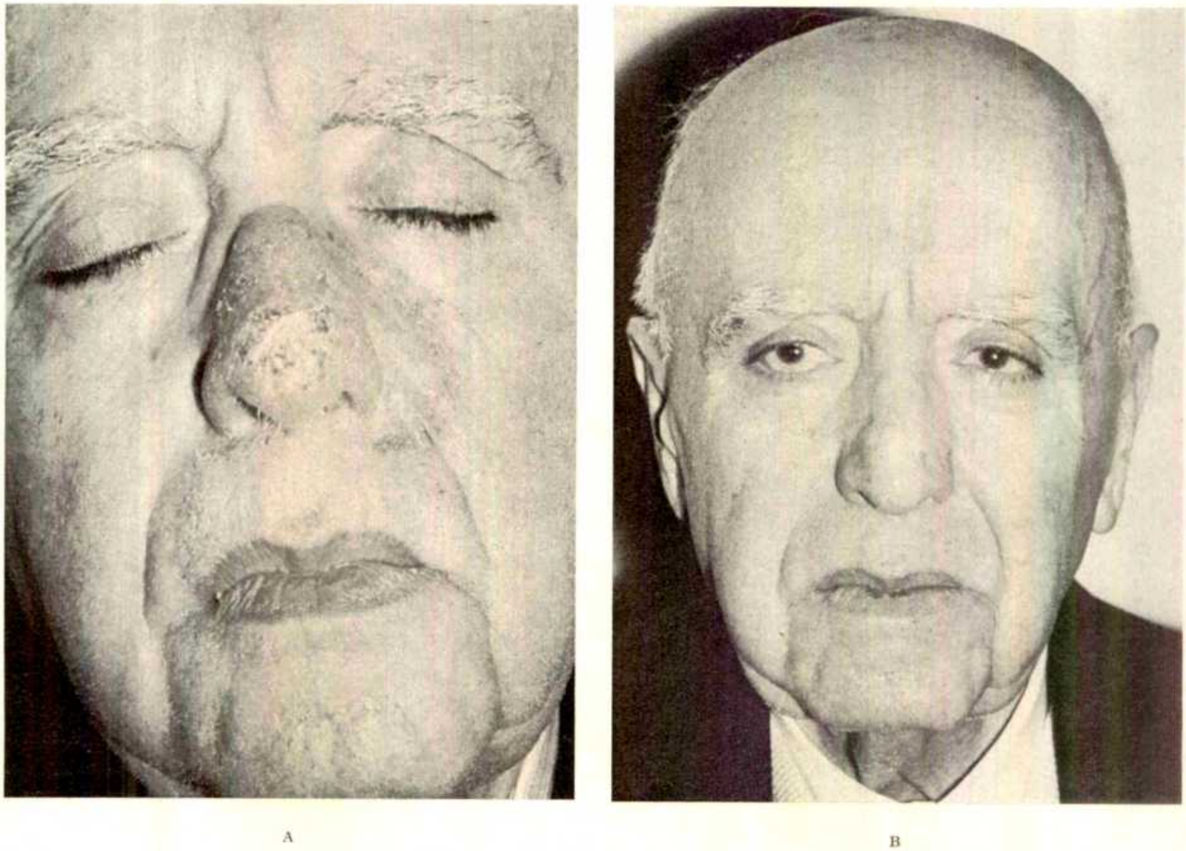


FIG. 1.
Rodent ulcer on nose and cheek.
(A) Erythema from treatment by ^{32}P applicator.
(B) Healed rodent ulcer following treatment.

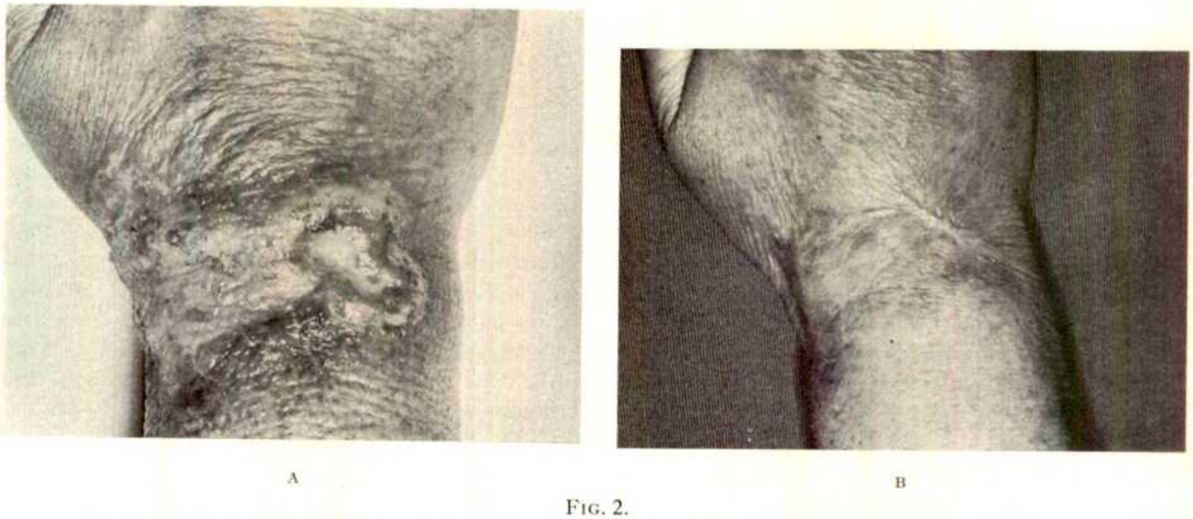


FIG. 2.
Squamous carcinoma of dorsum of the wrist: (A) before treatment; (B) after treatment by radiotherapy.

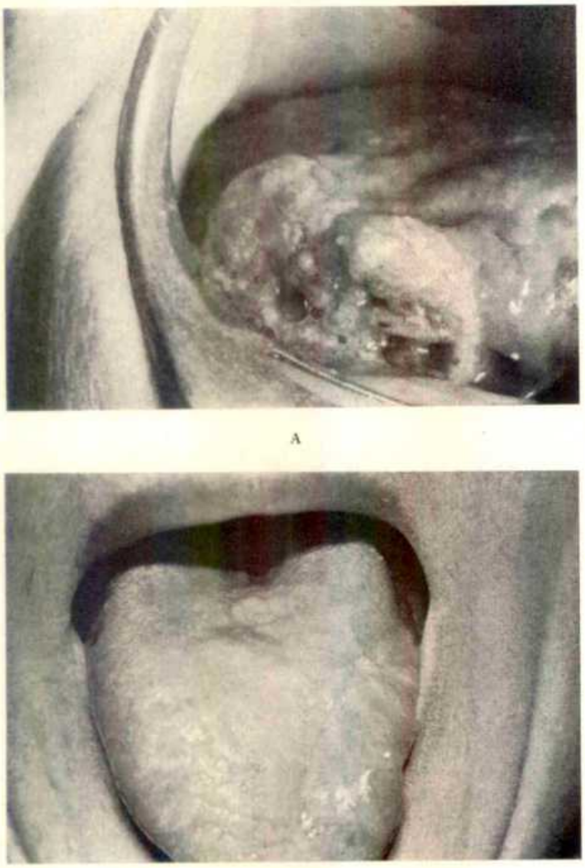


Fig. 3.

(A) Typical carcinoma of the lateral border of tongue.
(B) Tongue 32 years after treatment by radium needles.

surgical case can rarely be cured by radiotherapy (Fig. 3A and B).

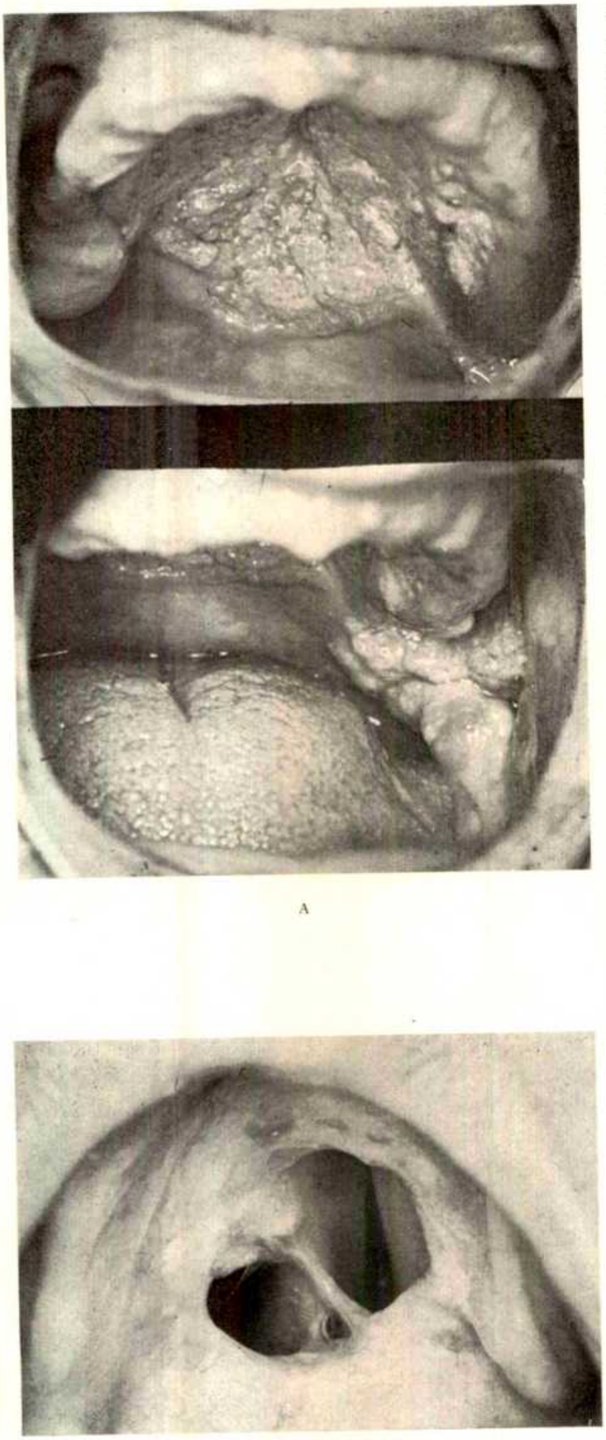
From the beginning of radiotherapy at The London Hospital, 40 years elapsed before the first combined clinic was started with the Department of Plastic Surgery. This proved so valuable that subsequently a combined clinic including radiotherapists, plastic surgeons and dermatologists was formed to consider all cases of skin cancer and to arrive at an agreed policy for treatment, not only of skin cancers but of buccal cancer also. Laryngeal and pharyngeal cancers were seen in conjunction with the surgeons of the E.N.T. Department. These combined clinics and others which were later established were of inestimable value to patients, and the sharing of clinical experience and the results of treatment improved survival and reduced morbidity due to both radiotherapy and surgery. In fact, a whole generation of medical students has grown up that has never seen radionecrosis.

Proliferative buccal neoplasms not amenable to any form of surgical treatment respond favourably to radiotherapy (Fig. 4A and B). Radiotherapeutic failures can be cured by surgery and live for many years free from recurrence.

Salivary gland tumours

In the 1930s salivary gland tumours were considered relatively unsuitable for surgical removal because of the high local recurrence rate. There was also a school of thought (McFarland, 1936) which taught that recurrence was more frequent in small rather than in large tumours and that surgical treatment should be delayed until the tumour was the size of a lemon. As a result many salivary gland tumours were enormous when first seen and were deemed inoperable, and referred for radiotherapy. Few of these large tumours responded dramatically to irradiation but some of the more cellular types did, and in others growth restraint with perhaps a 20% reduction in volume occurred. Burrows (1926) had shown that, even following recurrence, if the recurrences were excised and the region treated with interstitial radium sources the subsequent recurrence rate was markedly reduced. Four cases were described of mixed salivary gland tumours which were easily enucleated, and all four cases showed recurrence within a year. These recurrences were excised and the operation site treated with interstitial radium, and the same method was used with ten subsequent cases. Six years later there was no evidence of recurrence in any of these cases treated with surgery and interstitial implantation of radium needles. Another view was widely held that salivary gland tumours were multicentric in origin, and that therefore the only satisfactory treatment was total parotidectomy, an operation fraught with considerable risk to the facial nerve and a resulting facial paralysis. Patients who develop a facial palsy prior to treatment learn to live with their disability. Those who are paralysed as a result of surgery form a more difficult group and may require prolonged supportive psychiatric treatment. At all events it is important not to damage the facial nerve either by surgery or by interstitial irradiation. The first of these is a greater risk than the second. Any palsy which occurs immediately after surgery is due to the surgery; a radiation injury is not apparent for weeks or months. Patey's (Patey and Thackray, 1958) work on this problem showed by serial sections of surgically removed parotid tumours that the tumour was not multicentric, but that commonly multiple satellite nodules are attached to the tumour by a thin isthmus of tissue. He therefore advocated removal of the tumour with a cuff of normal gland; where this is feasible and the tumour is carefully dissected, the capsule is intact and there is no spill, mixed parotid tumours can be removed surgically. Thirty years ago the recurrence rate was high and the results achieved by Burrows (1926) encouraged the use of interstitial radium in most cases. The best practice was to implant the radium needles at the time of surgical removal of the tumour, so that the position of the needles relative to the facial nerve was known.

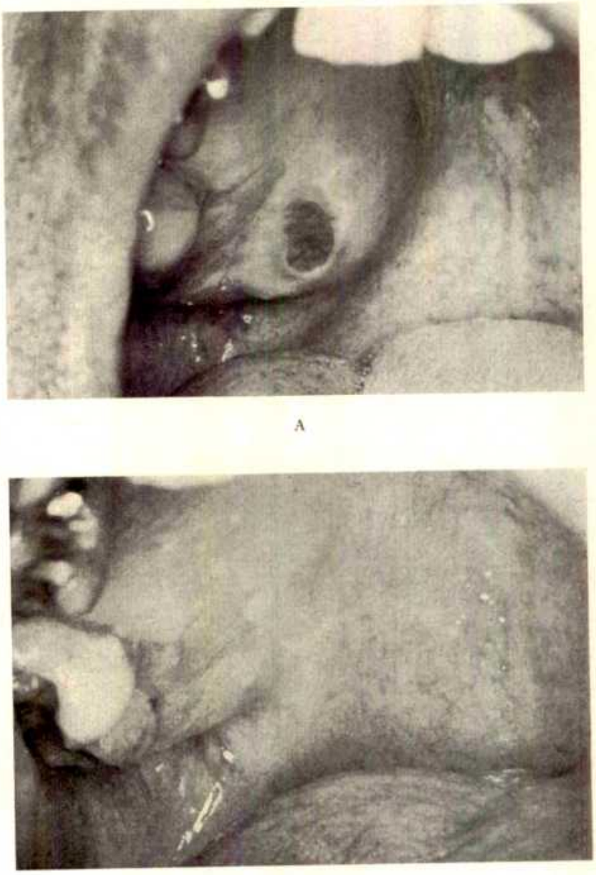
The response of salivary gland tumours to radiotherapy is variable. Tumours with a high mucinous content and marked connective tissue show a minimal response, but squamous carcinomas, cylindromas and tumours which exhibit marked cellularity may be very radiosensitive. The response of a cylindroma of the palate to external irradiation with


A

B

FIG. 4.

Squamous carcinoma involving hard and soft palates and buccal aspects of cheeks: (A) before treatment; (B) complete regression after extended X-irradiation. Palatal defects due to destruction of hard palate by tumour.


A

B

FIG. 5.

Cylindroma of the palate. (A) Before treatment; (B) after treatment by ^{60}Co γ rays using a wedged pair.

wedge fields is shown in Fig. 8a and b, and leaves no doubt about the response of this tumour.

The site distribution of 300 mixed salivary gland tumours treated in the Radiotherapy Department of The London Hospital is shown in Table I, and the age and sex distribution in Table II. During the same period 69 salivary gland carcinomas were seen and treated. The response to treatment of these two groups is shown in Tables III and IV. It should be noted that during this series radiotherapy was not given indiscriminately to all cases. Where the capsule was intact, a reasonable margin of normal tissue had been excised and there was no suggestion of spill or contamination, radiotherapy was withheld. In the last 20 years there has been immeasurable improvement both in surgical technique and in a greater appreciation of the surgical and pathological features of the problem, nevertheless there are still indications for post-operative radiotherapy as indicated below:

1. Recurrent tumour.
2. Unusual cellular activity in the adenoma.
3. Tumour adherent to facial nerve.
4. Spill of tumour cells.
5. Tumour impinging on pharynx.

Cancer of the larynx

In 1943 less than 15 years had elapsed since the publication of the classical paper by Finzi and Harmer on the radium treatment of carcinoma of the larynx. This paper was read at the Second International Congress of Radiology held in London in 1925. Finzi had been experimenting with radium since 1913 and it took him many years before he came to the conclusion that small amounts of radium should be buried in the tissues for a long time (Finzi and Harmer, 1928) and that larger doses of radium tended to cause necrosis and sloughing. It is important to realize that Finzi was treating cases with radium before the röntgen was defined; it is surprising, not that necrosis occurred, but that any cures were obtained, and yet he reported in his earlier paper seven cures of laryngeal cancer out of a total

TABLE I

Mixed salivary gland tumours (300). Site distribution

Mixed parotid tumours	247
Submandibular tumours	22
Palatal tumours	22
Upper lip	6
Nasal cavity	1
Tonsil	1
Sublingual	1
Total	300

TABLE II

Mixed salivary gland tumours (300).
Age and sex distribution

Years	Males	Females	Total
0–9	—	—	—
10–19	2	8	10
20–29	9	20	29
30–39	19	32	51
40–49	26	45	71
50–59	20	49	69
60–69	13	27	40
70–79	9	14	23
80–89	3	4	7

TABLE III

Salivary gland carcinoma (69).
Site and sex incidence

	Male	Female	Total
Parotid	22	26	48
Submandibular	5	7	12
Palatal	4	5	9
Total			69
Treatment offered and results			
Surgery			11
Surgery and radiotherapy			30
Radiotherapy			24
Untreated			4
Total			69
No sign of recurrence			27
Alive, with metastases			2
Died			40
Alive for five years			9

TABLE IV

Mixed salivary gland tumours (300). Treatment offered and results

Total number of cases	300
Treatment	
Surgery	58
Surgery plus radium needles	157
Surgery plus D.X.R.	64
Surgery plus cobalt	10
D.X.R.	4
No treatment	7
Total	300
Results	
Dead	19
Untraced	12
Residual tumour	7
No sign of recurrence	262

of 15 cases, which compares very favourably with a later series published by Harmer of 118 cases and an overall survival of 53 or 47%, when dosage definition and measurement had been accurately established (Harmer, 1953). In a total of 284 cases of laryngeal cancer treated at The London Hospital between 1943 and 1953 which included all cases referred of whatever stage the five-year survival figures were 59% with intrinsic cancer and 15% with extrinsic cancer. Twenty years later the survival of earlier stages continues to improve. In T.1 cases with a mobile cord the total survival was 91%, but this included 11.5% of laryngectomies. The results according to stage are shown in Table V.

From these figures it is clear that the indication for immediate laryngectomy for an extensive T.3 cancer of the larynx should improve the survival figures and reduce the morbidity due to irradiation.

The survival figures for supraglottic carcinoma treated by irradiation alone in this latter period were 52.9% for five years. The marginal zone involving the aryepiglottic fold showed no improvement with a five-year survival of 14%.

Cancer of the oesophagus

There has been a remarkable improvement in the response to treatment of cancer of the oesophagus in the last 20 years. During the period when orthovoltage was the only available radiotherapeutic treatment it was difficult to obtain a cancericidal dose to lesions situated deeply in the thorax, and attempts were made to supplement the external irradiation with intra-oesophageal rubber tubes containing a line source of radium. This was always hazardous; Souttar's inimitable phrase that "the oesophagus is like a tube of wet blotting paper" highlights just how great is the risk of perforation. The results of treatment were poor; at the beginning of treatment the patient was ill and emaciated and had difficulty in swallowing, and at the end of treatment there was the additional risk of increasing breathlessness due to irradiation of the lung, as six or perhaps seven fields were required with the external irradiation technique. To start with a patient who could not swallow and end up with one who could neither breathe nor swallow, was scarcely a satisfactory response. Many radiotherapists had abandoned all hope of improving the treatment of cancer of the oesophagus until the results of rotation therapy were reported from Copenhagen by Nielson (1945). The patient was treated sitting in a rotating chair, and when his arms came into the beam he was told through a speaking grill to lift his arms and place his hands on the top of his head. Alternatively, he could support his arms by grasping with his hands a cross-piece suspended from the ceiling. The patient swallowed a little barium porridge which served to make the site of the neoplasm visible on a screen, and by slight adjustments of the chair or stool the treatment beam was centred on the oesophagus during the whole rotation.

TABLE V

RESULTS OF TREATMENT OF CARCINOMA OF LARYNX BY STAGE. ALL CASES TREATED AT THE LONDON HOSPITAL, 1953–1973

Glottic	5-year survival
T.1 No Mo	91.0%
T.2 No Mo	67.7%
T.3 No Mo (including 3 T.3 Nl Mo)	40.7%
	Percentage laryngectomies
T.1	11.5%
T.2	17.6%
T.3	48.1%

Nielson's results of 25% alive and free from obstructive symptoms at one year and 15% alive at two years were much better than previous results achieved by multiple field techniques. He also reported three five-year survivals and one at ten years in cancer of the upper third of the oesophagus. As the average age of his material was 65.7 years, two years' freedom from obstructive symptoms was a most encouraging palliative result.

Telecobalt therapy which started in 1956 further improved the palliative treatment of oesophageal cancer. Pearson's (1966) epoch-making paper showed what remarkable results could be achieved with megavoltage treatment for what had been an almost incurable condition a decade earlier. Radical megavoltage radiotherapy could now produce cure rates of 25% five-year survivals for the post-cricoid region, 23% for lesions between 18–29 cm from the incisor teeth, and 17% for lesions beyond 30 cm.

Treatment may be followed by a stricture at the site of the lesion and clinically the recurrence of difficulty in swallowing may suggest recurrent neoplasm, but oesophagoscopy may reveal a stricture which can be dilated. Dilatation carries a minimal risk in skilled hands.

Few palliative procedures evoke such favourable and grateful comments from patients' relatives as irradiation for cancer of the oesophagus. Symptoms are relieved, swallowing is restored, and death when it comes is usually quick and merciful.

Cancer of the breast

The teaching on the treatment of cancer of the breast in the 1930s was clear cut. If the tumour was operable a radical mastectomy was advised and if inoperable palliative radiotherapy of a desultory kind was given. The röntgen had only recently been introduced, the total dose given was low, of the order of 2000 R in three weeks and the appearance of a skin erythema was a sign that treatment should be stopped. The idea behind the radiotherapeutic approach was, as has been described earlier, control of the cancer and not cure. Surgeons were generally of the opinion that although cure was unlikely in any event, it was slightly more probable if the surgical technique was extensive and radical, rather than localized and conservative. The concept that malignant disease is rarely cured except when the primary is confined to the tissue of origin had neither been enunciated nor conceived. Because of the reluctance to rely on radiotherapy alone, the selection of cases suitable for surgery was not so rigorous as subsequently and as a result the recurrence rate in the skin flaps was high. Results of combined surgery and radiotherapy published from Stockholm (Westermark, 1930) suggested that the five-year survival figures could be improved from 20% to 40%, and even more remarkable improvement was reported by Pfahler (1931). Post-operative irradiation with a modified Holfelder technique became fairly general. One great advantage which occurred was a marked reduction in chest wall recurrence, and *cancer en cuirasse* ("the breastplate of cancer") which had been a common occurrence became much less so. The radiotherapists of this period spent much of their time indulging in what was called "a chasing technique"—treating and chasing an ever-widening area of skin metastases involving first one side of the chest then the other and eventually the whole trunk and elsewhere. Much earlier, papers had been published to show that if a patient with breast cancer received radiotherapy the prognosis was less favourable than for those who did not (Perthes, 1920). Further evidence disproved Perthes' original opinion.

The first breakthrough came when Halstead (1898), who was the first to dissect the supraclavicular lymph glands, realized that involvement of supraclavicular glands heralded widespread dissemination of disease and precluded radical surgery. Forty years later, in 1941, McWhirter started a collaborative treatment policy of simple mastectomy combined with post-operative radiotherapy with a large group of surgeons in South East Scotland, and he later reported a 10% increase in absolute five-year survivals when radical mastectomy was replaced by simple mastectomy and radiotherapy (McWhirter, 1955).

In the United Kingdom since the mid-1950s there has been a continuous change from radical to simple mastectomy, and arguments in favour of both methods have been vigorously advanced; as far as numbers are concerned the simple mastectomists are now more numerous than the radical mastectomists. The survivals in Stage I are clearly best in the radical mastectomy series as 87% five-year survivals have been published by Cade (1948) and 86% by Gordon-Taylor (1938). In his Skinner Lecture in May 1947 Richards (1948) produced evidence in favour of post-operative selected radiotherapy in Stage I cases, and in more advanced operable cases pre-operative radiotherapy and in some cases post-operative radiotherapy. With inoperable cases treated radically by radiotherapy he indicated that five-year survivals of the order of 35–43% could be expected. Westermark (1930) had claimed from the Radiumhemmet that post-operative irradiation improved the five-year survival to 29.3% compared with 20–23% after surgery alone, and that pre- and post-operative radiotherapy further increased survival to 40%; his figures in conjunction with Richards' formed a firm basis for the value of radiotherapy in the treatment of breast cancer. Recently the whole position has been challenged and radiotherapy has been stated again, as it once was in the 1930s, to be positively harmful, and that axillary dissection may be harmful also by reducing the immunological defence mechanism against the dissemination of the disease. Before radiotherapy was available radical surgery had been the only treatment, as failure to dissect the axilla led inevitably to a fixed inoperable axillary mass with pain and oedema of the arm. When the value of radiotherapy was established simple mastectomy could safely be offered as an alternative method of treatment. The latter day tendency to advise the minimum of surgery is deplorable and already there is evidence of increasing frequency of local recurrence in cases where post-operative irradiation has not been prescribed. Apart from well-founded statistical evidence of improved survival in mammary cancer when surgery and radiotherapy are combined, the greatest single advance in the last 30 years has been the reduction of local recurrence in the skin flaps. Until some other form of treatment emerges, radiotherapy has a well established place in the treatment of breast cancer in reducing the morbidity due to the disease, improving survival figures, and palliatively for the relief of bone pain and to minimize and prevent paraplegia due to vertebral metastases.

Hodgkin's disease

When I first specialized in radiotherapy over 30 years ago, Hodgkin's disease and the various tumours of the lymphoid tissue were regarded as very sensitive to deep X-ray therapy but, and especially with Hodgkin's disease, recurrence was inevitable and at autopsy there was always evidence of residual disease. It was, however, accepted by some radiotherapists that lymphosarcoma in a solitary site was capable of permanent cure either by radiotherapy or by surgery and examples of survival for 20–40 years had been recorded. With Hodgkin's disease there were no records of long-term survival and it was considered that as recurrence would take place it was important not to exceed the local tissue tolerance so that a remission when once achieved could be followed by a further regression of glandular masses when treated subsequently. It was rare, therefore, to prescribe a tumour dose in excess of 2000 R. Survival of cases of reticulum celled sarcoma of bone had already been reported for periods as long as 14 years (Parker and Jackson, 1939). A series of 475 cases of reticulosis treated in the Radiotherapy Department of The London Hospital between the years 1944 and 1956 and followed up for a further ten years until 1966 was analysed by Hope-Stone (1969) and the results are shown in Tables XI, XII, XIII, XIV and XV.

The comparison of the five-year survival rates for various stages of Hodgkin's disease, lymphosarcoma and reticulum celled sarcoma are shown in Figs. 10, 11 and 12. The dramatic response to external irradiation of glandular enlargement in these conditions is well known.

Until the provocatively phrased title of the paper, "The cure of Hodgkin's disease" by Easson and Russell (1963) made an appropriate impact, I had never believed that Hodgkin's disease was curable, and I was agreeably surprised to find that in my own department the five-year survival figure of Hodgkin's disease in most stages, except Stage III, was slightly in excess of 50%.

In 1969 it was difficult to see how the prognosis in the reticuloses could be improved, and yet today the realization by the use of lymphography that failure in Stages I and II is due in 50% of cases to abdominal disease, and by the use of laparotomy and the introduction of combination chemotherapy, the prognosis in Stages I, IIa and IIb and IIIa may approach 70% disease free.

TABLE XI

HODGKIN'S DISEASE—THE LONDON HOSPITAL.
FIVE-YEAR SURVIVAL IN RELATIONSHIP TO STAGE

Stage	No.	No. alive 5 years	% alive 5 years
I	51	27	53%
IIa	32	18	56%
IIb	57	29	51%
IIa and IIb	89	47	53%
I, IIa, IIb localized	140	74	53%
III generalized	94	6	6.35%

TABLE XII

LYMPHOID FOLLICULAR RETICULOSIS.
FIVE YEAR SURVIVAL—THE LONDON HOSPITAL

Stage	No. treated	No. surviving 5 years	% 5-year survival
I and II	10	4	40%
III	13	4	31%

TABLE XIII

LYMPHOSARCOMA—CLINICAL STAGING AND
FIVE YEAR SURVIVAL

Stage	No. treated	No. surviving 5 years	% 5-year survival
I	25	17	68%
II and IIb	26	13	50%
I, IIa and IIb	51	30	58.5%
III	48	6	12.5%

TABLE XIV

RETICULUM CELL SARCOMA. STAGING IN RELATIONSHIP
TO FIVE YEAR SURVIVAL—THE LONDON HOSPITAL

Stage	No. treated	No. surviving 5 years	% 5 year survival
I	32	21	66%
II and IIb	18	5	27.5%
I, IIa and IIb	50	26	52%
III	45	1	22%

TABLE XV

COMPARISON OF FIVE YEAR WITH TEN YEAR SURVIVALS
IN LOCALIZED RETICULOSES—THE LONDON HOSPITAL

	% 5-year survival	% 10-year survival
Hodgkin's	53%	33%
Lymphosarcoma	63%	31%
Reticulum cell sarcoma	52%	50%

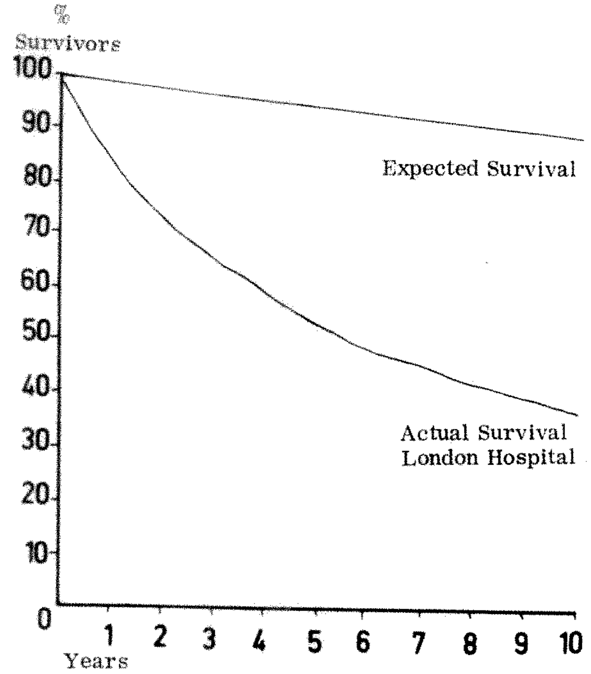


Fig. 10.

Hodgkin's disease—localized cases. Comparison of crude survival rate with the expected survival rate in the normal population.

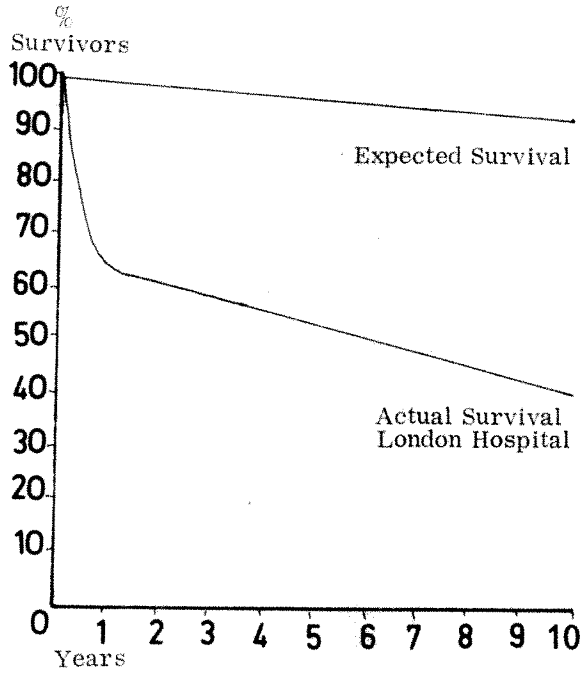


Fig. 12.

Reticulum cell sarcoma—localized cases. Comparison of crude survival rate with the survival rate in the normal population.

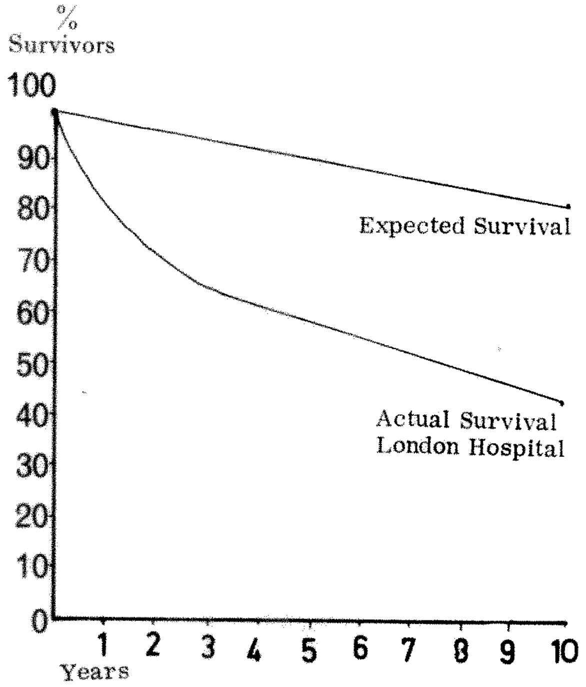


Fig. 11.

Lymphosarcoma—localized cases. Comparison of crude survival rate with the expected survival rate in the normal population.

Bone sarcoma

Before a Department of Orthopaedic Surgery was established at The London Hospital, it was difficult to induce the general surgeons to carry out amputation for bone sarcoma, and most cases were treated primarily by radiotherapy. During this phase, I treated 18 bone sarcomas with no long survivals. Most of them died within a year. The only available form of irradiation was deep X ray (180–200 kV), and frequently symptomatic relief was obtained. With recurrent symptoms and increasing size of tumour, repeated courses of treatment were prescribed leading inevitably to local radionecrosis. It was not uncommon to be forced to advise amputation in a terminal phase in order to relieve pain and to obviate nursing difficulties even in the presence of chest metastases.

In 1940 Albert Ferguson reviewed the first 400 cases of osteogenic sarcoma in the registry of bone sarcoma of the American College of Surgeons, cases with inadequate data or seriously disputed diagnosis being excluded. Of 258 cases treated by amputation, the five-year survival rate was 8% after early amputation (within six months of onset) and 29% after late amputation (more than six months after onset).

The treatment of breast cancer must be based on its clinical type, as some decision must be taken after the size and operability are assessed and before the histology is available. Cade's description of six types is invaluable:

1. Paget's disease of the nipple.
2. The bleeding nipple.
3. Scirrhous carcinoma.
4. Atrophic scirrhous.
5. Encephaloid carcinoma.
6. Acute carcinoma.

Sir James Paget (1874) described an eruption, "on the nipple and areola" . . . 'In the majority it had the appearance of a florid, intensely red, raw surface, very finely granular, as if nearly the whole thickness of the epidermis were removed; like the surface of a very acute diffuse eczema or like that of an acute balanitis . . . But it has happened that in every case which I have been able to watch, cancer of the mammary gland has followed within at the most two years, and usually within one year." It follows from this remarkably accurate description that the treatment should be removal of the whole of the mammary disc. If this includes the lower axillary nodes so much the better as histological examination will help to exclude nodal metastases. If, as is usual in the absence of an underlying mammary tumour, these are not present, no further treatment is necessary. Despite Sir James Paget's clear description of the onset of an underlying tumour, 70 years later it was still not common for Paget's disease of the nipple to be treated surgically by local excision of the eczematous and ulcerated area of the nipple and areola.

The bleeding nipple may include four histological varieties:

(a) Duct papilloma
(b) Duct carcinoma
(c) Intraduct carcinoma
(d) Intraduct epithelial hyperplasia.

The duct papilloma may be demonstrated radiologically; as the duct carcinoma is very rare local excision is indicated. The intraduct carcinoma involving the smaller lactiferous ducts may be treated by simple mastectomy, but in the elderly there is a place for sector mastectomy and sector mastectomy is the treatment of choice for intraduct epithelial hyperplasia.

Scirrhous carcinoma which is the commonest of all types has given rise to the most diverse opinions on its treatment and management. Where the tumour is small, 1–1.5 cm diameter, Geschikter (1945) states that metastases have occurred to axillary lymph nodes in 25% of cases, and when the average size of the primary tumour is 5 cm or more and the history is a year or more, metastases have occurred in nearly all cases and to internal viscera in 90% of cases.

If these statements are accepted as correct it follows that the prognosis is established when the patient is first seen and that long term survivals in breast cancer are rarely to be found where the classification exceeds Stage I. On the other hand well-authenticated survivals for 40 years and more have occurred in Stage II with histologically proved axillary glandular metastases. It is difficult, therefore, to deny a patient with a small primary carcinoma the advantage of a radical mastectomy. It is also to be expected that in large series of patients the results of treatment will, in most cases, be independent of the method used and dependent mainly on staging and its distribution. It is unlikely, therefore, that either retrospective studies or prospective clinical trials are likely to shed much light on the problem.

It has been pointed out (Richards, 1948) that individual differences in skill and criteria of operability affect survival figures. In his large series of 1189 cases operated upon by over 30 different surgeons, the five-year survivals varied from 77% to 17%. Although this is rarely commented on it must be the common experience of most radiotherapists that some surgeons get better results than others. A further difficulty in arriving at a definite opinion is illustrated by the figures in Table VI. The survival figures can even vary with a single surgeon (Butler, 1974). The table shows how the survival figures are better during his earliest period as a surgeon when

TABLE VI

Results of surgery in carcinoma of breast (Butler 1974)

		Five-year survival	Ten-year survival
First hundred			
Radical mastectomy	83		
Stage 1	35	87%	68%
Stage 2	48	75%	42%
Simple mastectomy	17	No survivors	
Second hundred			
Radical mastectomy	62		
Stage 1	37	77%	54%
Stage 2	25	56%	30%
Simple mastectomy	38	39%	32%
Third hundred			
Radical mastectomy	44		
Stage 1	26	65%	
Stage 2	18	55%	
Simple mastectomy	56	39%	

radical mastectomy was the operation of choice and that the figures are slightly worse during a later period. Throughout the period the results of simple mastectomy were poor compared with radical mastectomy.

Testicular tumours

Levitt (1930) commented on the radiosensitivity of seminomata in these words: "These growths are extremely radiosensitive—in many cases, indeed, exceeding lymphosarcoma in the rapidity with which they disappear upon exposure to X rays. Even when metastases have occurred X rays should be applied, and in many advanced cases of growths of this type with abdominal masses X-ray therapy has resulted in marked improvement or even in complete disappearance of the growth for a period of months or years." A patient treated in the Radiotherapy Department of The London Hospital in 1943 with an abdominal metastatic mass extending two fingers' breadths above the umbilicus and with bilateral lung metastases is still, in 1975, alive and well and free from any evidence of neoplasm. The value of post-operative radiotherapy for seminoma of the testes was well established among radiotherapists over 40 years ago, and simple orchidectomy followed by irradiation of the abdominal glands was considered to be the treatment of choice. In an earlier period, following the opinion of Chevassu (1906), radical orchidectomy was advised as the results of simple orchidectomy were so poor. By the 1930s, however, most surgeons were agreed that the best treatment was simple orchidectomy and post-operative irradiation of the abdominal glands. In the Skinner Lecture in 1946 Gordon-Taylor asserted that radiation therapy was the preponderant factor in the treatment of testicular tumours. All were agreed on the value of radiotherapy in the treatment of seminomata, but there was disagreement as regards teratomata although Stanford Cade and Allchin believed that radiotherapy combined with surgery improved the results of treatment of teratomata compared with surgery alone. This point of view influenced the treatment of teratomata at The London Hospital, and from the 1940s the pelvic nodes as well as the abdominal nodes were irradiated. Published results (Gordon-Taylor and Wyndham, 1947) for testicular tumours are shown in Table VII. Further improve-results were published (Snelling and Cones, 1952; Prossor, 1959) during the next decade. In North America (Patton *et al.*, 1960), the view was advanced that surgical removal of abdominal glands, especially for those testicular tumours which are radioresistant, would improve prognosis.

TABLE VII

TESTICULAR TUMOURS, GORDON-TAYLOR'S SERIES

	All cases	Seminoma	Teratoma
Total No.	636		
1-year survival	62%	61%	55%
3-year survival	47.7%	48%	33%
5-year survival	44.5%	43%	18%
10-year survival	23.9%	27%	15%

Embryonal carcinoma of the testes had been classified by Ewing in 1911, but in 1951 Muir's *Textbook of Pathology* did not include it. In the 1958 edition, embryonal carcinoma was first mentioned as one of the three important tumours of the testes: seminoma, embryonal carcinoma and teratoma. The London Hospital material which had previously been classified as seminoma or teratoma was re-graded according to the classification of Dixon and Moore, seminoma, embryonal carcinoma, teratoma, teratocarcinoma, chorioncarcinoma and others. An analysis of this material was carried out (Hope-Stone *et al.*, 1963) and indicated five-year survival figures in the case of teratocarcinoma of 68.7% when treated with simple orchidectomy and radiotherapy, compared with 54.5% treated by Patton with orchidectomy and lymphadenectomy. There is, however, no doubt that prolonged survival has occurred in those from whom positive lymph nodes were removed by dissection nor is there any question that surgical removal can be followed by cure. It is important to remember that lymphadenectomy was supplemented by radiotherapy to a substantial dose in all but six of the 243 cases treated by Patton with lymphadenectomy. At any rate, it was felt that the evidence as it stood did not encourage a change and that the treatment policy for all varieties of testicular neoplasms should be orchidectomy followed by radiotherapy.

The next great step forward was the classification of testicular tumours by Collins and Pugh (1964). This led to the significant discovery of the variation in prognosis of teratomas and the improved prognosis of M.T.I.A., as compared with M.T.I.B. and M.T.A. tumours (Blandy *et al.*, 1970).

The improved pattern of survival in seminoma and teratoma of the testes is seen in Tables VIII and IX.

Carcinoma of the bladder

Before 1950 I had seen only two cases of bladder cancer respond completely to external irradiation with orthovoltage X rays (200–250 kV). Most cases treated radically required a six-field technique using

TABLE VIII
THE LONDON HOSPITAL 1950–1968.
SEMINOMA—SURVIVAL RATE

Clinical stage	3 years			5 years		
	No.	Surv.	%	No.	Surv.	%
1	81	75	93	74	68	92
2	10	9	90	7	6	86
3	14	1	7	13	1	7

TABLE IX
THE LONDON HOSPITAL 1950–1968.
TERATOMA SURVIVAL RATE

	Clinical stage	3 years			5 years		
		No.	Surv.	%	No.	Surv.	%
M.T.I.A.	1	30	27	90	24	21	88
	2	1	0	0	0	0	0
	3	0	0	0	0	0	0
M.T.I.B. and M.T.A.	1	16	4	25	17	3	18
	2	8	2	25	8	0	0
	3	11	0	0	10	0	0

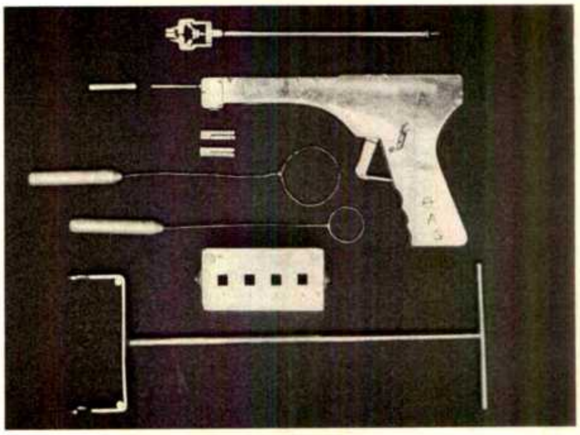


FIG. 6.

Gun for implantation of radon seeds, including magazines, protective carrying block and flexible metal ring for locating the area of implantation.

10×8 cm or 8×6 cm fields, in order to obtain a cancericidal dose at the bladder. Moist desquamation skin reactions occurred at all the treated areas. This reaction was uncomfortable for the patient and gave rise to nursing difficulties more especially as the customary treatment at that time was by applications of gentian violet lotion. Earlier papers had been published on the treatment of bladder cancer by radium (Hutchinson, 1935; Paterson, 1941). Jacobs (1947) had reported the results of bladder cancer treated by open operation and implantation of radium needles and showed that of 47 patients treated 21 had survived six years or more. There are difficulties in inserting straight radium needles into a curved viscus like the bladder and a further disadvantage was the need to leave the suprapubic wound open for several days so that the radium needles could be removed. Tantalum wire was considered but it seemed preferable to use a radioactive source that did not need to be removed post-operatively, and so it was decided to use radon seeds. With the collaboration of Professor Victor Dix and Mr. Gerald Tresidder, surgeons of the Urological Department of The London Hospital, a combined clinic was established in 1950 to assess all cases of bladder cancer and decide on the method of treatment. All tumours which could be satisfactorily treated with closed cystodiathermy were excluded together with tumours with an estimated base exceeding 4 cm diameter. Tumours which cystoscopically or on rectal examination were larger than these dimensions were also excluded, as were those with extravesical spread. If, at open cystotomy, the tumour was too large to be treated with interstitial radon seeds, radon seeds were used as radiological markers to assist in subsequent planning and localization prior to treatment by external irradiation. As there was no satisfactory radon seed introducer available, I designed a radon seed gun which was made in The London Hospital workshop by Mr. E. L. J. Penfold and is shown in Fig. 6, together with the radon seed magazines, protective carrying block and flexible metal rings to determine accurately the shape and area of implantation. The diathermy snare is passed over the tumour (Fig. 7), the loop being held by the index finger of the left hand, and the snare is drawn tight. This method leaves a coagulated area on the base of the bladder in which the muscle fibres can be seen (Fig. 8). An X ray of the radon seed implant is shown in Fig. 9. The results of this method of treatment appear in Table X and show five-year survival of 78% in papillary differentiated carcinoma and a ten-year survival of 59%. The solid anaplastic tumours show a much poorer survival of 30% at five years and 13% at ten years. Telecobalt therapy was not available until January 1957 and was then the treatment of choice for most solid tumours and especially tumours too large to be treated by open cystodiathermy and radon seed implant. When radon seeds were no longer available they were superseded by radioactive gold grains. In the last five years the use of this method of

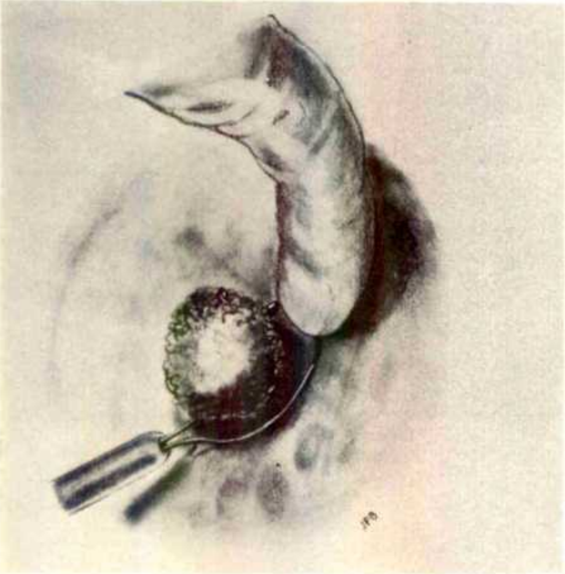


FIG. 7.
Diathermy snare being tightened around base of tumour in bladder.

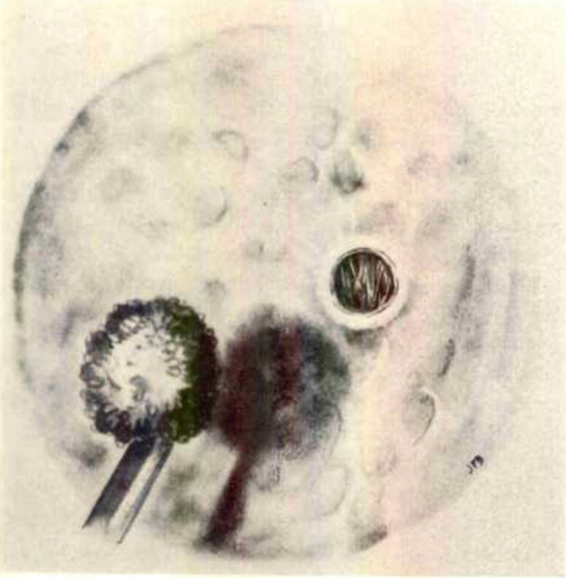


FIG. 8.
Removal of tumour and showing bladder muscle fibres in the base.

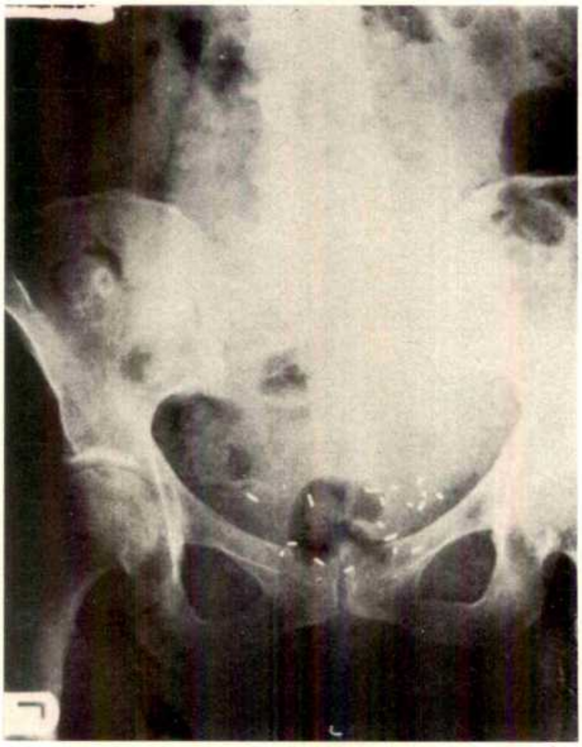


FIG. 9.
Radiograph of radon seed implant for carcinoma of bladder.

TABLE X

FIVE AND TEN YEAR SURVIVAL OF PATIENTS WITH CARCINOMA OF BLADDER TREATED WITH DIATHERMY AND RADON SEEDS

All cases		350
5 years	51%	
10 years	35%	
Papillary differentiated		136
5 years	78%	
10 years	59%	
Solid anaplastic		111
5 years	30%	
10 years	13%	

treatment has declined due to the introduction of improved resecting cystoscopes; larger tumours than previously are amenable to closed cystodiathermy. The response to external irradiation has shown a marked improvement over orthovoltage treatment, and some hundreds of tumours have been followed up with dramatic local regression and long-term survival free from recurrence. The full assessment of this response is at present undergoing analysis.

In cases where the histology suggested a lower degree of malignancy, 14% survived early amputation and 41% survived late amputation, and where the degree of malignancy was high, 4% survived early amputation and 37% delayed amputation. Even if cases of low malignancy were excluded, 24% of the delayed amputations survived. From these results Ferguson argued against early amputation. Excision before amputation also appeared to improve survival. He also stated that the results of amputation either early or late could not be shown to be affected by biopsy, fracture, incision or drainage. Haste to amputate, he concluded, tends to assure the death of the patient. He also stressed what was my own experience, that only rarely has a patient detectable metastases before amputation, though the disease may have been present for months or even years, and yet metastases are regularly detectable within a few months after amputation. Only eight out of a total of 258 cases in the American Registry had detectable metastases before amputation. In explanation of his analysis of bone sarcoma cases Ferguson postulated an early active phase, and a later quiet phase when tumour cells were likely to be absent from the blood stream. It seemed to me more likely that tumour cells were always present in the peripheral blood, but that the primary exercised an inhibiting effect which was some function of the growth rate of the primary. The rapid growth of secondaries in the lungs following amputation suggested a sudden availability of the precursors of cell growth for the secondaries when the primary was removed. Pre-operative irradiation by slowly reducing the activity of the primary over a series of days might produce a more favourable phase in which to amputate, and furthermore cells which disseminated after the start of irradiation were much less likely to produce viable secondaries, and if they did the growth doubling characteristics of the secondaries might be changed. Clinical confirmation of this view has been obtained from many of the failures and one of the survivors of the series of bone tumours: one of the patients who had a pre-operative dose of 10000 R in 1957 developed chest metastases three years later. He is still alive and well after a successful lung resection.

In a large series of 118 five-year survivals from the records of the American registry of bone sarcoma (McDonald and Budd, 1943), 21 of which were chondrosarcoma, 97 survivors out of a group of 654 who had been treated five years previously or longer gave a five-year survival figure of 14.8%. Platt's (1947) surgical series of 161 cases of bone sarcoma of all types including chondrosarcoma showed 23 survivals over five years or 14.3%, and osteolytic osteogenic sarcomas accounted for five of those 23 cases. Tudway (1953) reported a five-year survival of 12.1%. Coley and Harrold (1950) from the Memorial Hospital, New York, have reported 59 five-year survivals out of a total of 252 cases or 23.5%.

Comparisons between different series is difficult and cases of chondrosarcoma probably creep into most series of osteosarcoma, but enough has been published to show that at least four out of every five patients do not survive five years. To improve survival rate it would seem not unreasonable to test the value of higher pre-operative doses of irradiation. No definite evidence of the value of pre-operative irradiation could be adduced from previously published figures, but at least it had not been shown to have a deleterious effect.

There was fairly general agreement that doses less than 3000 R had little demonstrable effect on bone tumours; doses between 3000 R and 4000 R produced temporary inactivity, and higher doses up to 6000 R more prolonged inactivity, while doses of 8000 R or more were required to sterilize bone tumours. In 1950, I started to treat a series of bone sarcomas with pre-operative irradiation and amputation. A dose of 1000 R was given daily in ten fractions to a total dose of 10000 R. A dose of this order can be given without causing local discomfort or systemic effect. Amputation was usually performed within one or two days of finishing the course of radiotherapy. It is too long to wait for a week after such a pre-operative dose, as the skin at this time may develop a painful bullous reaction. It is important to obtain the patients consent, and to impress upon him that he may not change his mind on the question of amputation once the radiotherapy has been started.

Apart from osteosarcoma, which I shall return to later, there are a few interesting cases to record. Figure 13 is a radiograph taken in 1947 of a female, aged six, showing an osteolytic lesion involving the left scapula close to the glenoid cavity. A biopsy was performed and reported as a Ewing's tumour. A course of radiotherapy was given at 200 kV. The appearance of the scapula two years later is shown in Fig. 14. Figure 15 shows post-radiation atrophy 25 years later over the left deltoid region. There is no loss of power or movement of the left shoulder joint, and the atrophy is mainly of the subcutaneous fat rather than of muscle.

Figure 16 shows a chondrosarcoma of the right superior pubic ramus which was successfully removed by local resection, and the patient, the mother of a large family, walked on two legs for the next 13 years.

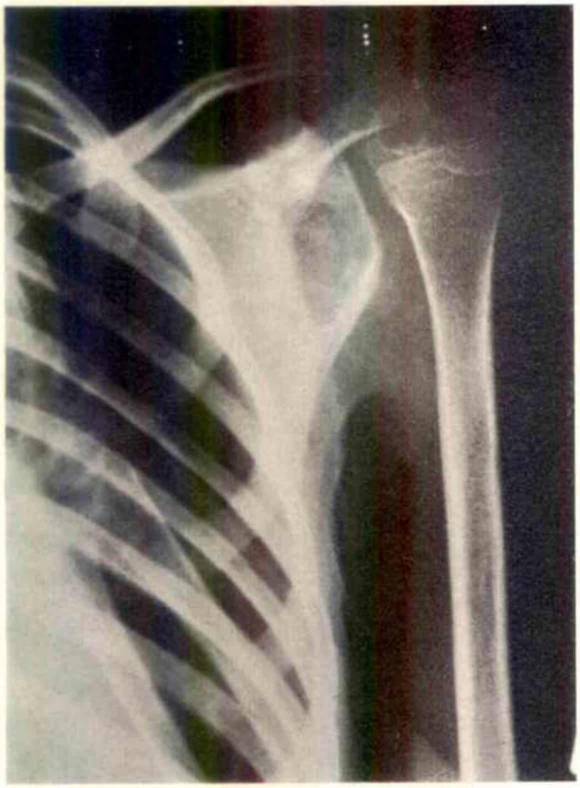


Fig. 13.
Ewing's tumour of left scapula of girl aged six.

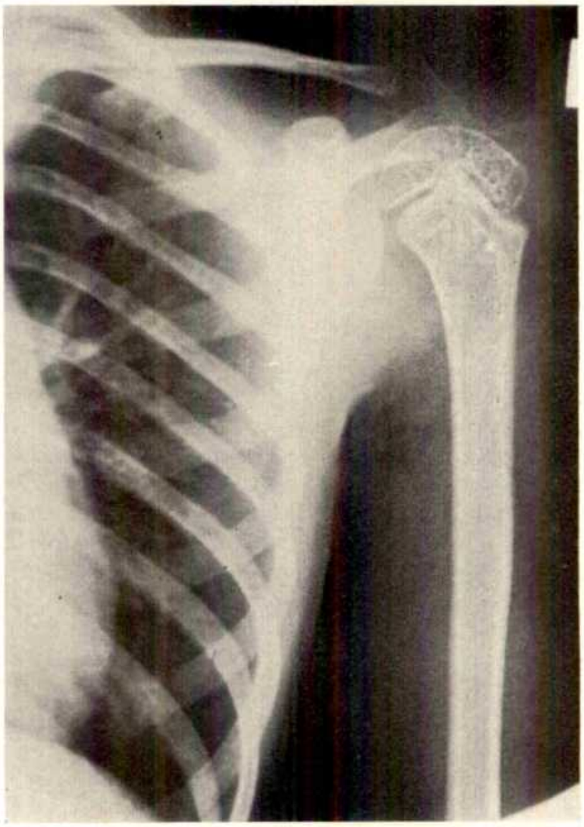


Fig. 14.
As Fig. 13 but two years after treatment.

Myxosarcoma is sometimes surprisingly radiosensitive. A small boy, aged seven, presented with a large tumour of the cheek about the size of an adult fist. It was regarded as inoperable. Drill biopsy was performed and the histological report was myxosarcoma. As the tumour was increasing in size a radical course of irradiation was started on a telecobalt unit with a wedge pair of fields. Somewhat surprisingly, at a dose of 3000 R in two weeks, the tumour had regressed completely. At this stage it was decided that to proceed to a radical and curative dose would produce a subsequent facial hemi-atrophy, and so the referring surgeon was invited to re-assess the problem of operability. The tumour appeared to have arisen from the zygomatic arch, and by removing the zygoma, zygomatic arch and the floor of the orbit the residual neoplasm was completely excised and proved to be eminently operable. Figure 17A shows the boy, aged nine, two years after the operation. In 1968, when he was aged 17, and the growth of his facial bones was considered to have stopped, a bone graft was inserted and Fig. 17B shows the

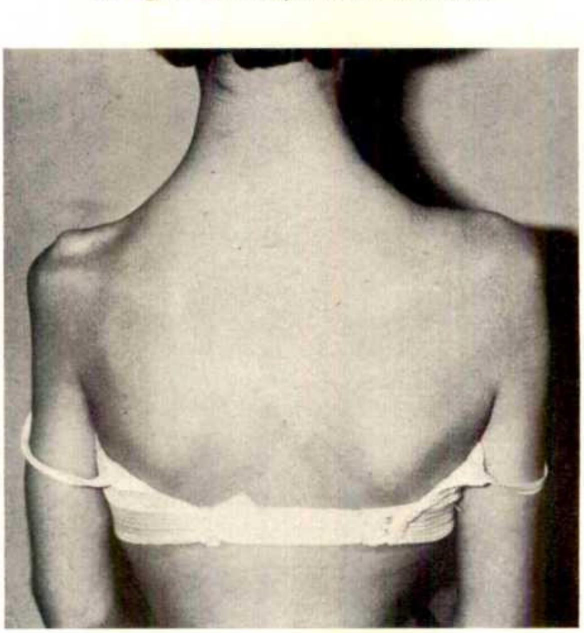


Fig. 15.
Situation of the patient of Fig. 13, 25 years after treatment.

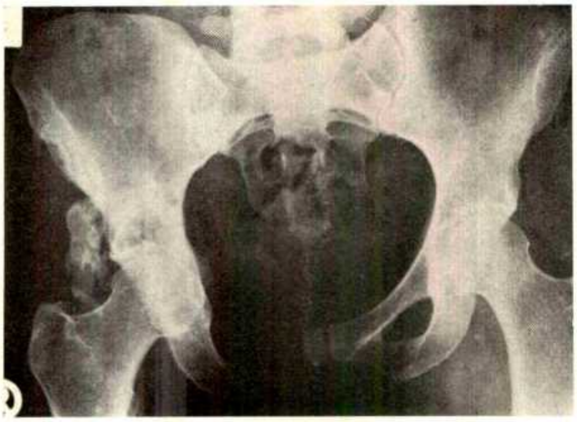
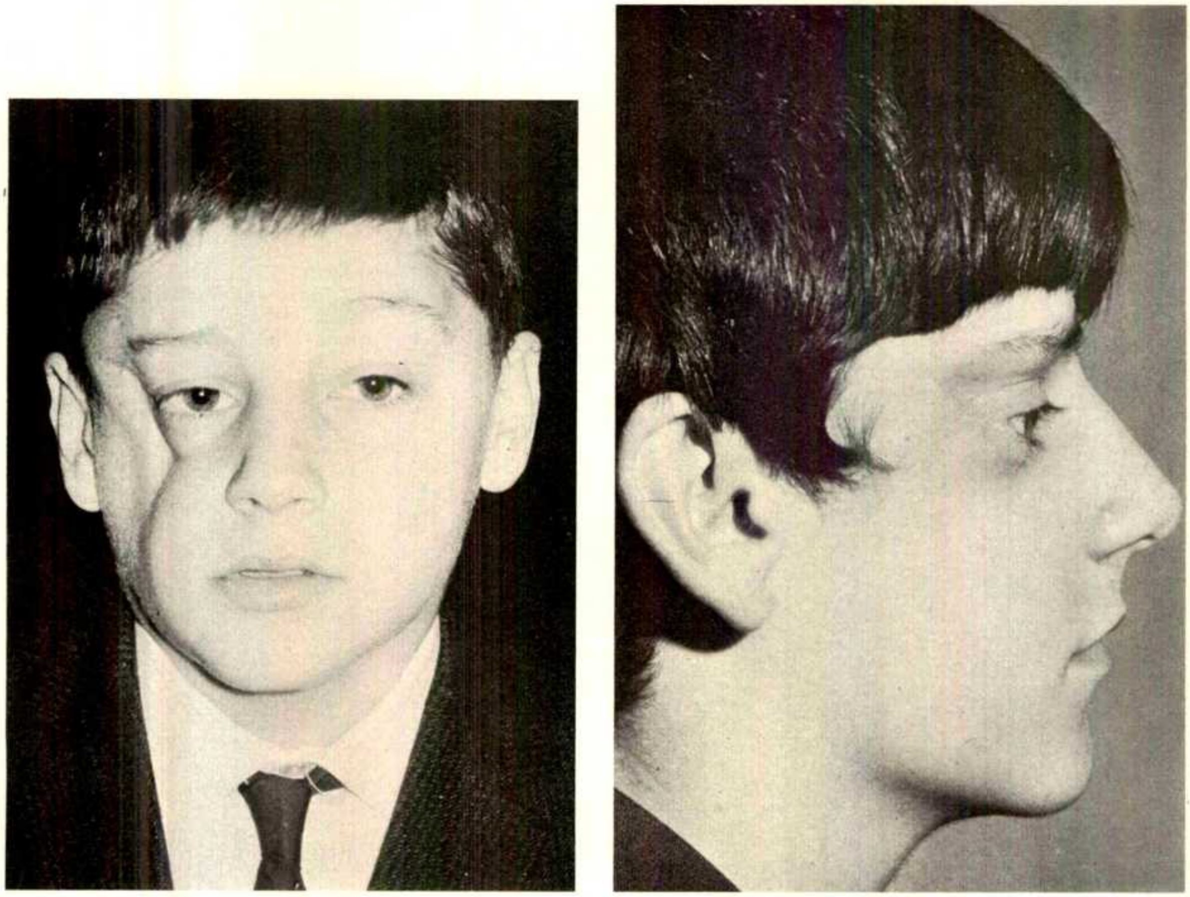


FIG. 16.
Chondrosarcoma of superior pubic ramus after excision.

satisfactory result. I have seen this patient during 1975 and he is well and free from recurrence, but he is developing a radiation cataract.

The distribution of a personal series of malignant tumours is shown in Table XVI. This series excluded all cases of Ewing's tumour, reticulum celled sarcoma or myeloma. The general policy was to prescribe post-operative irradiation to a dose of 10 000 rad in ten fractions to all osteosarcomas which had previously been diagnosed histologically following open surgical biopsy. Chondrosarcomas where operable were resected without pre-operative irradiation, and post-operative irradiation was only considered if there was a risk of local recurrence. The results of treatment are shown in Table XVII.

In these cases treated with pre-operative radiotherapy and immediate amputation, the five-year survival figure was 57.7%.



A B

FIG. 17.
Myxosarcoma of zygomatic arch treated by surgery and pre-operative radiotherapy. (A) Two years after treatment. (B) Ten years after treatment and following bone graft and plastic repair.

Brain tumours

There has been little advance in the radical treatment of malignant brain tumours in the last 30 years, although the palliative treatment has improved. Before finishing this wide-ranging survey of the response to treatment of malignant disease, I should like to refer to the remarkable improvement in the treatment of medulloblastoma by my colleague, Dr. H. F. Hope-Stone. By carefully designing the irradiation of the cerebral contents and the vertebral axis in a single volume rather than treating the skull and spinal cord with multiple fields, a very significantly improved prognosis of medulloblastoma has been achieved as shown in Table XVIII.

TABLE XVI

Malignant bone tumours at The London Hospital 1950–1970

Osteosarcoma	44
Chondrosarcoma	23
Sarcoma on Paget's disease	9
Malignant osteoclastoma	3
Synovioma	2
Total	81

TABLE XVII

Results of treatment of bone tumours at The London Hospital

Chondrosarcoma		
5-year survival	13/23	=56.5%
Sarcoma on Paget's Disease		
5-year survival	0/9	=0%
Osteosarcoma		
X-ray treatment	12	None survived
Amputation only	6	None survived
Pre-operative radiotherapy and amputation	26	15 survived
Total	44	15 survived

TABLE XVIII

Results of irradiation for medulloblastoma

Time period	No. of cases	Type of X-ray treatment	5-year survivals	
			No.	%
1943–1950	16	Partial or matched	1	6
1950–1968	24	Homogeneous	14	59

With the advances in chemotherapy and the emergence of oncology as a speciality with many facets, a new era is beginning in the treatment of cancer. Because of this it seemed to me of some value to record the changes and advances in radiotherapy from its earliest times to the present. Despite the improvement in prognosis in various sites, the greatest advance in my lifetime has been a reduction in morbidity due to treatment.

ACKNOWLEDGMENTS

I should like to thank the following people for their kind assistance: the staff of the Radiotherapy Department of The London Hospital; Dr. H. F. Hope-Stone for placing at my disposal analysis of cases treated; Professor John Blandy for the results of treatment of testicular tumours; Mr. R. Ruddick of the Medical Photographic Department for his invaluable contribution in preparing illustrations and tables; Miss S. Gibby for her help in providing me with illustrations and tables, and my secretary Mrs. Gill Price for her generous co-operation in typing the manuscript.

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Book review

Recent results in cancer research—cancer chemotherapy. By A. Clarysse, Y. Kenis and G. Mathe, pp. xx + 566, illus., 1976 (Springer-Verlag), $39.40.

This is the first English edition of a book which is recognized as a landmark in the development of medical oncology, Mathe and Kenis: *La Chimiotherapie des Cancers;* it should be on the bookshelf of every radiotherapist. These are strong words, but in contrast to the mammoth multi-author tomes which have become the standard works of trans-Atlantic oncology, this is a coherent, balanced presentation. It puts in remarkably good perspective the respective roles of surgeons, radiotherapists and medical oncologists in the treatment of both early and advanced cancers.

The section on basic cell biology is as clearly written as this reviewer has seen and far better than in any well known introductory radiotherapy text. The section on classification and modes of action of chemotherapeutic agents is up to date. The specific discussions of principles of cancer chemotherapy and the frank assessment of achievements and failures are good, and although this tends to be a bit encyclopaedic in presentation it is none the less readable and direct, and remarkably free of jargon and self-delusion.

The major fault of this volume is that it is reproduced from typescript and the typeface chosen is remarkably hard on the eyes in its reduced size. There is a wealth of tabular material and a bibliography which is commendably up to date (fully inclusive to 1975). Only the subject index leaves something to be desired, as it is idiosyncratic in its inclusion or exclusion of the trade names by which many of the chemotherapeutic agents are marketed and suffers from an excess of cross references to other headings.

All in all, however, this English edition, like its French language predecessor, is truly a landmark.

R. J. Berry

1977, *British Journal of Radiology*, *50*, 400–403

A 20-year prospective follow-up of childhood hiatal hernia*

By R. Astley, M.D., F.R.C.P.E., D.M.R., F.R.C.R., I. J. Carré, M.A., M.D., F.R.C.P., D.C.H., and R. Langmead-Smith, S.R.N.

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ABSTRACT

A long-term prospective follow-up of 113 children with vomiting due to a small hiatal hernia is described. When reviewed by the same clinical and radiological observers 20 or more years later, over 90% of unoperated non-stricture patients were asymptomatic whereas only 44% of the stricture and/or surgically treated group were without symptoms.

Half or possibly more of the asymptomatic patients still had a hernia and it is possible that these may suffer a recurrence of symptoms later in adult life. The loculus of thoracic stomach tended to retain the same shape; there was a slightly better prognosis for the locular type of hernia compared with the tubular type.

Complicating oesophageal strictures can decrease or disappear without surgery other than dilatation; the results of treatment by radical surgery were disappointing.

There is need for an even more prolonged follow-up into later adult life.

It has been shown that the majority of children with vomiting due to a small hiatal hernia lose their symptoms spontaneously (Carré *et al.*, 1952; Astley and Carré, 1954; Carré, 1959), a process that is expedited by postural treatment (Carré, 1960, 1971). However, despite an absence of symptoms, the hiatal hernia can still be identified radiologically in many of these children (Carré and Astley, 1960). The later history of these subjects as they pass into adult life is still unknown. The present study was, therefore, undertaken to obtain information about this aspect of the condition. We had a unique opportunity in this respect because the same two observers were personally responsible for the clinical (I.J.C.) and radiological observations (R.A.), both at initial diagnosis and at follow-up examination 20 or more years later. Moreover, both observers had retained their original detailed personal records of each patient, additional to the ordinary hospital case notes. The third member of the team (R.L.S.) was responsible for tracing the patients and persuading them to attend for clinical and radiological study.

MATERIAL AND METHODS

One hundred and forty six children seen at the Birmingham Children's Hospital between 1950 and 1955 in whom a definite diagnosis of a small hiatal hernia was made were listed for review. These consisted of children appearing *de novo* during this period but also included a number recognized retrospectively from amongst undiagnosed long-standing "vomiters" and children with oesophageal strictures who had attended hospital before 1950. There was, therefore, an excess of patients with strictures and/or persisting symptoms, compared with an unselected spectrum of the disease. During the three years of the project, 113 patients out of the 146 were traced (77%). Ninety-five were interviewed and 92 of these were examined radiologically by barium swallow. Clinical information about the remaining 18 patients was obtained from interviewing mothers and/or by correspondence with the subjects themselves.

Patients on review were classified into two groups, *i.e.* those *without* and those *with* symptoms. Asymptomatic patients were defined as those with no symptoms in excess of occasional heartburn or vomiting that was associated with a major dietary indiscretion or, alternatively, heartburn or water brash that occurred less often than twice a month.

Radiological findings were graded as positive or negative according to whether or not a loculus of stomach was identified in the chest. When it was not possible to decide this with absolute certainty and by strict criteria, findings were classified as "plus–minus". Gastro-oesophageal reflux was graded similarly, "plus–minus" implying that reflux was either a minimal trace or reflux of air only.

The shape of the thoracic stomach was also noted. Where this was much the same calibre as the oesophagus, without much constriction at the gastro-oesophageal junction, it was called "tubular"; where it formed a more expanded region it was called "locular". The tubular type included cases that might well have been mistakenly labelled in infancy as so-called "chalasia". The shape of the herniated stomach is apt to vary during examination, particularly according to the degree of distension with contrast, and these labels were only applied when appearances were consistent.

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*Based on papers read to a joint meeting of the Royal College of Radiologists, British Institute of Radiology and Radiological Section of the Royal Society of Medicine at Birmingham in April 1976, and the European Society of Paediatric Radiology at Stockholm in May 1976.

RESULTS

A preliminary report of our findings has been published (Carré *et al.*, 1976). The majority of the subjects reviewed (91 out of 113 or 81%) were asymptomatic. In 27 there were complicating oesophageal strictures and/or modification of the natural history by surgical treatment; if these patients are excluded, the proportion of asymptomatic subjects is increased to 92%, *i.e.* 79 out of 86.

Radiological examination was performed on 92 out of the 113, consisting of 71 of the 86 unoperated non-stricture patients and 21 of the 27 stricture and/or surgically treated group. These two groups are considered separately.

Unoperated, non-stricture group

The radiological findings in these subjects are shown in Table I. It is seen that when there were no symptoms, a hernia was still detected in about half the subjects (Figs. 1 and 2). The proportion could be as high as two thirds, if the less certain "plus–minus" cases were also to be included.

The shape of the thoracic stomach in the initial and follow-up examinations was classifiable, with the reservation mentioned previously, in only 46 cases (Table II). There was a tendency for the loculus of thoracic stomach to retain the same shape; it did not increase in relative size but either remained the same or became less detectable. Relating the original shape to subsequent progress showed that 24 out of 26 of the locular type and 15 out of 20 of the tubular type were now asymptomatic.

Strictures and/or surgically treated group

These form a heterogeneous group as shown in Table III. The six without strictures who had a

TABLE I
RADIOLOGICAL FINDINGS IN UNOPERATED, NON-STRICTURE GROUP (71 SUBJECTS)

		Symptom free	*With symptoms*
Hernia	+	32	3
	±	11	2
	−	21	2
Reflux	+	7	0
	±	4	1
	−	53	6

TABLE II
SHAPE OF HERNIA (46 SUBJECTS)

Initially	*Follow-up*	
Locular (26)	Locular	14
	Tubular	3
	±	3
	Normal	6
Tubular (20)	Locular	1
	Tubular	10
	±	2
	Normal	7

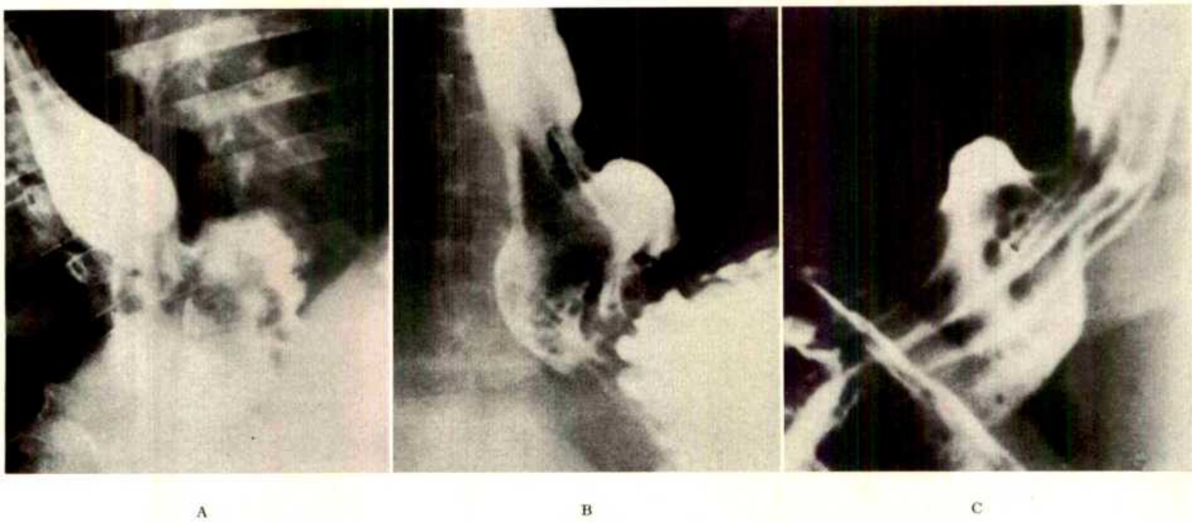

FIG. 1.
(A) Age 4 years. (B, C) Age 25 years. Asymptomatic.

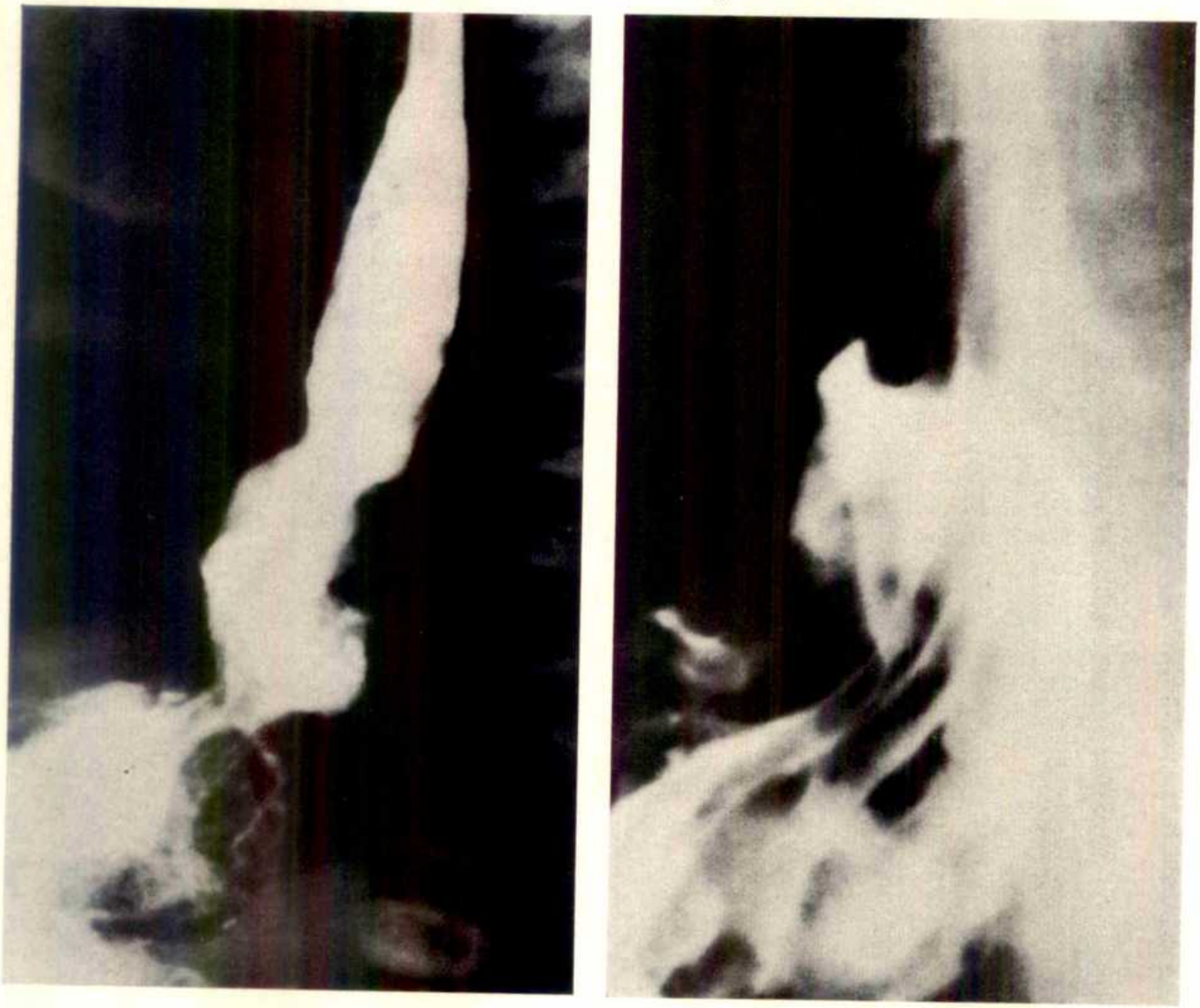

Fig. 2.
(A) Age 8 days. (B) Age 22 years. Asymptomatic.

simple hiatal repair were all asymptomatic. Of five examined radiologically, two had a residual hernia and one also showed reflux. Amongst those with strictures but no surgery (other than dilatation), one out of six (probably three out of ten on the evidence of examinations at other hospitals) had *no* stricture at follow-up (Table IV); of the seven subjects with a residual stricture, three, because of careful attention to their diet, complained of only occasional transient discomfort. Amongst the seven who underwent

TABLE III
Strictures and/or surgical operation (27 (21*) cases)

Surgical repair (without stricture)	6(5)
Oesophageal stricture	21(16)
No operation	10(6)
Repair of hernia	4(3)
Major surgery	7(7)

* figures in brackets indicate numbers examined radiologically at follow-up.

TABLE IV
Subjects with strictures but no surgery (10 subjects)

Stricture disappeared	3
Stricture decreased	2
State unknown	1
Deteriorated	4

radical surgery, four had either an oesophago-gastrostomy or oesophago-jejunostomy and all four still had symptoms with a mild oesophageal stricture. Three had colon transplants; none had a stricture and two were asymptomatic.

DISCUSSION

The high incidence of asymptomatic subjects 20 or more years after the diagnosis of a small hiatal hernia in childhood supports earlier observations that the prognosis for symptomatic relief in this condition is very good (Carré, 1959, 1971). When patients with oesophageal strictures in childhood and/or surgical treatment are excluded, the figure for asymptomatic subjects is over 90%.

The disappearance of symptoms was not dependent upon the disappearance of the hiatal hernia because in at least half (and possibly nearer two thirds) of the asymptomatic unoperated cases a hernia was still detected radiologically, although the incidence of reflux was low (Table I). This persistence of an anatomical abnormality suggests that in at least some of these subjects there is the possibility of a return of symptoms in later adult life. An even longer period of follow-up will be necessary to confirm this.

There was a tendency for the loculus of thoracic stomach to retain the same shape and the hernia did not increase in relative size but either remained the same or became less detectable. A slightly higher proportion of the locular type of hernia, as opposed to the tubular, became asymptomatic.

It is not the purpose of this paper to compare the relative values of conservative and surgical treatment. Indeed, the heterogeneous nature of the relatively small group who had oesophageal strictures and/or received surgery prevents firm conclusions. In retrospect there is no very good reason to believe that the six children without oesophageal strictures who had simple hiatal repairs were necessarily any more severely afflicted than many in the non-surgical group. While the six children without oesophageal stricture who had simple hiatal repairs were all asymptomatic, so were 92% of the much larger number of non-stricture cases who had no surgery.

It is perhaps unwise to place too much emphasis on the poor results seen after the treatment of oesophageal strictures by major surgical procedures since these were performed many years ago and techniques may have improved since. However, it should be noted that some oesophageal strictures can disappear or decrease without surgical treatment other than dilatation and that patients, by adopting appropriate eating habits, can lead relatively symptom free lives despite some residual oesophageal narrowing. Furthermore, it must be remembered that while the number of strictures in the present series is high because of the method of case selection, the incidence of reflux stricture in the natural course of the disease is under 5% (Carré, 1959).

ACKNOWLEDGMENTS

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Intracranial extravasation of contrast medium during carotid angiography

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(*Received December, 1976*)

ABSTRACT

The results of 5184 carotid angiograms were reviewed and five cases of intracranial extravasation of contrast medium were found. In two cases an aneurysm ruptured during angiography and extravasation into the subarachnoid space was seen. In one case contrast medium leaked from an angiomatous malformation into the subdural space. The fourth case was a patient who had suffered closed head trauma. Here extravasation was seen deep within the brain. The fifth case illustrates two forms which extravasation from meningeal arteries may take. The incidence and prognostic significance of this finding in different conditions are discussed.

Intracranial extravasation of contrast medium during carotid angiography is rare, but over the past few years it has been reported in association with a number of conditions. This finding, which implies active bleeding, has been seen in subarachnoid haemorrhage from ruptured aneurysms and in one case of bleeding from an angiomatous malformation (McLennan *et al.*, 1974). Extravasation of contrast medium from cerebral vessels following trauma has been seen in 12 cases and it is well documented in extradural haemorrhage following traumatic rupture of meningeal vessels. Extravasation following "spontaneous" intra-cerebral haemorrhage associated with hypertension is said to be relatively common (Bergstrom and Lodin, 1967; Huckman *et al.*, 1970; Leeds and Goldberg, 1970; Yamaguchi *et al.*, 1971; Kowada *et al.*, 1972; Mizukami *et al.*, 1972).

Previous reports of extravasation of contrast medium are either single case reports or describe several cases with a common aetiology, giving little indication of the incidence of this finding in neuroradiological practice. We reviewed the findings of 5184 angiograms performed in Oxford between 1970 and 1976 and describe the five cases of contrast medium extravasation found in this series.

Our angiography was undertaken with either Mimer I or Mimer III equipment with Schönander AOT or Puck Serial Film Changer. A focal spot of 1 mm was used and a minimum of eight films were taken in both A.P. and lateral projections. Most angiography was by direct puncture, but trans-femoral catheterization was also used. Subtraction and magnification techniques were used as required.

CASE REPORTS

Case 1

A 46-year-old woman suddenly developed severe headaches and vomiting. Seven days later she developed neck stiffness and was admitted to her local hospital where a lumbar puncture showed uniformly blood stained cerebrospinal fluid with xanthochromia. On transfer to Oxford she was found to have minimal right hemiparesis with extensor plantar responses. Right sided carotid angiography with cross compression showed a small aneurysm just distal to the origin of the left anterior cerebral artery with spasm of the adjacent vessels (Fig. 1). This aneurysm was seen to be intact, but when left carotid angiography was performed by direct puncture it was seen to have ruptured with extravasation of contrast medium under the frontal lobe and along the Sylvian fissure (Fig. 2). Extravasation appeared on the first film of the series and was still visible at the end of the series 12 seconds later.

After angiography the patient became densely hemiplegic with severe dysphasia. She rapidly deteriorated and died one day later. Autopsy confirmed the rupture of the left anterior cerebral artery aneurysm.

Case 2

A 45-year-old woman was admitted with a history of deep unconsciousness. On admission she was slightly dysphasic with right facial weakness and no other signs. A lumbar puncture showed blood stained xanthochromic cerebrospinal fluid. Right carotid angiography by direct puncture was performed and showed an aneurysm of the middle cerebral artery and another at the origin of the posterior communicating artery. The latter aneurysm appeared intact on the first film (Fig. 3) but extravasation of contrast medium from it was seen on the second and subsequent films of the series (Fig. 4). Following the rupture of the aneurysm, she became deeply hemiplegic but gradually recovered over the next 48 hours. Left carotid angiography then showed two further aneurysms on the left side. A craniotomy was performed and the aneurysms of the right

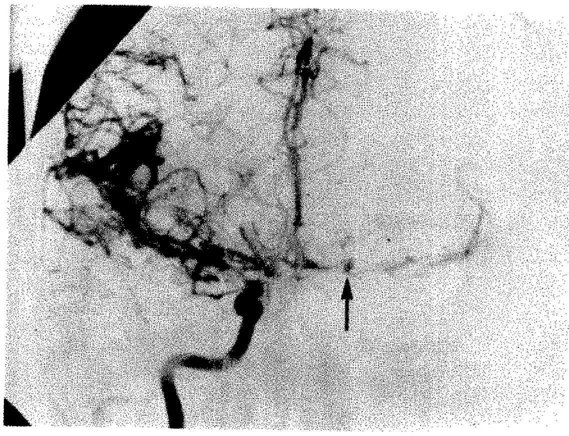
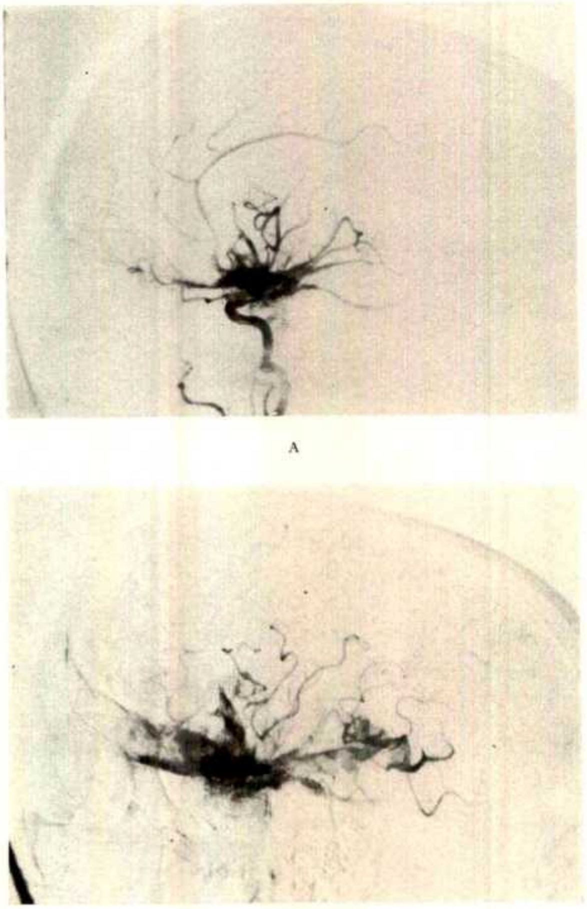


FIG. 1. *Case 1.*

A.P. right carotid arteriogram showing an aneurysm of the left anterior cerebral artery (arrow) filled by cross circulation.



A

B

FIG. 2. *Case 1.*

(A) Early arterial phase of left carotid angiogram showing extravasation of contrast medium.

(B) Late arterial phase of same examination showing further spread of extravasation.

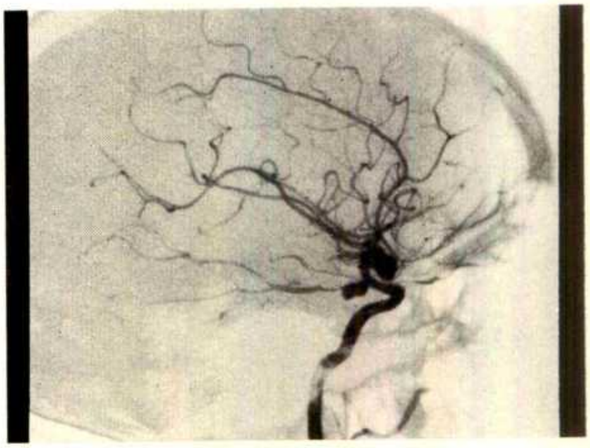


FIG. 3. *Case 2.*

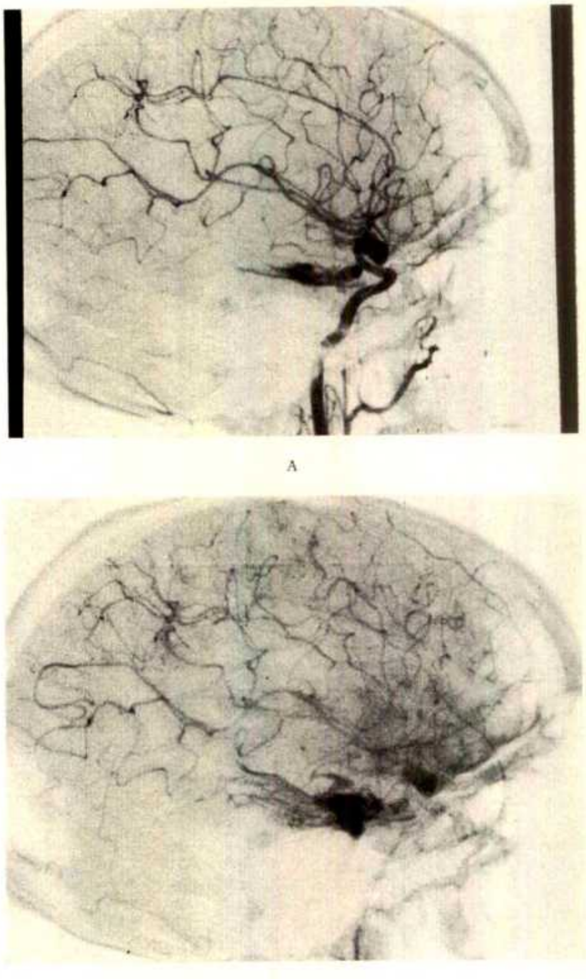
Early arterial phase of right carotid angiogram showing intact middle cerebral and posterior communicating artery aneurysms.

middle cerebral and right posterior communicating arteries were clipped. The patient made a good recovery.

Case 3:

A 15-year-old boy suddenly developed severe head-ache and vomited. Over the next hour and a half his level of consciousness rapidly deteriorated. On admission to hospital he was unconscious with Cheyne-Stokes respiration. He had a fixed dilated pupil on the right with left facial weakness and a spastic left hemiparesis.

A right carotid angiogram was carried out about three hours after the onset of symptoms and showed a large avascular mass in the right frontal region displacing adjacent



A

B

FIG. 4. *Case 2.*

(A) Later film showing rupture of posterior communicating artery aneurysm with extravasation.

(B) Further spread of extravasated contrast medium.

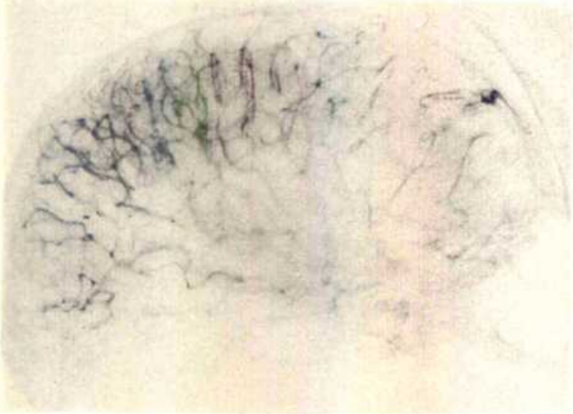


FIG. 5. *Case 3.*

Late arterial phase of right carotid angiogram showing a collection of abnormal vessels in a relatively avascular area in the frontal lobe.

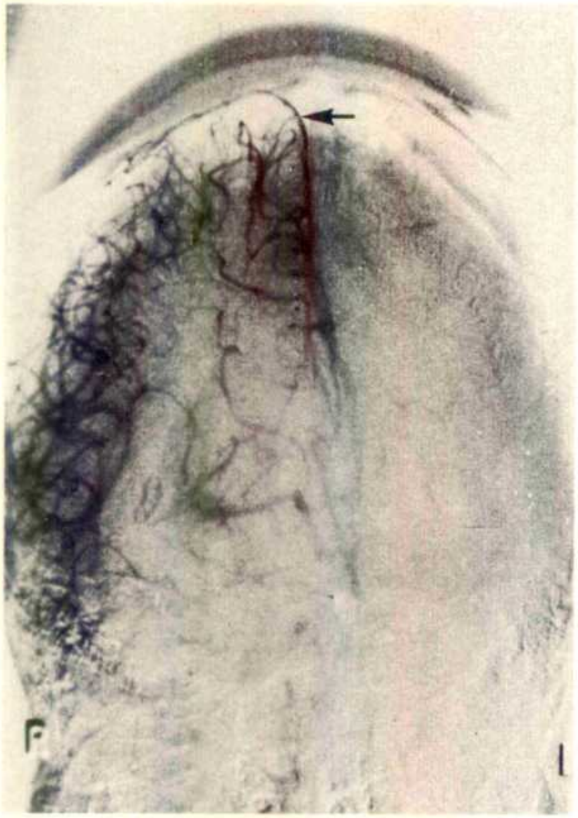


FIG. 6. *Case 3.*

Towne's view of the same examination showing contrast medium extending in a thin rim around the medial and superior surface of the cerebral hemisphere (arrow).

vessels (Fig. 5). A small collection of tortuous vessels lying near the middle of the frontal lobe was seen. On the Towne's view contrast medium was seen to spread from this region into the subdural space and along the medial aspect of the right cerebral hemisphere (Fig. 6). This appeared on the first film of the series and persisted until the last, 12 seconds later. These findings indicated a small angiomatous malformation which had produced a large frontal haematoma spreading into the subdural space.

This was confirmed at operation when a large clot was aspirated. A large vein was seen in the region of the malformation draining arterialized blood into the sagittal sinus. The right frontal lobe was resected. Post-operatively the spasticity resolved and over the next few weeks the patient recovered completely.

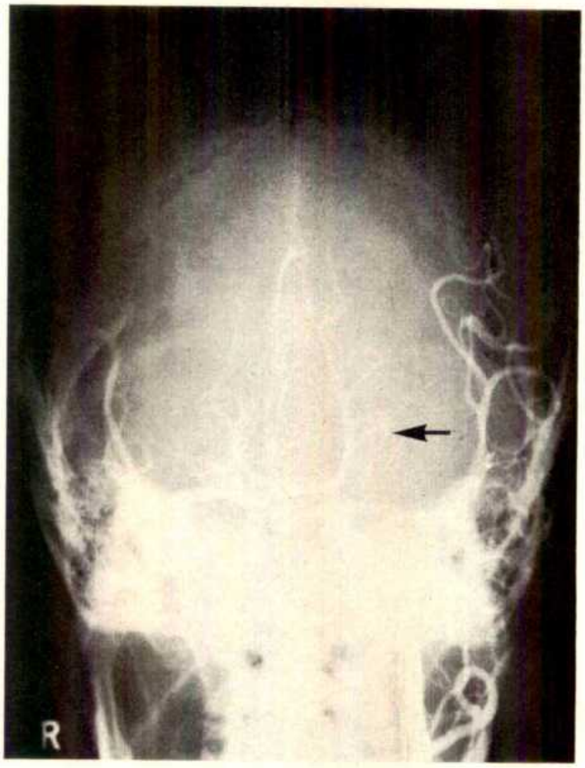


FIG. 7. *Case 4.*

Arterial phase of left carotid angiogram showing contrast medium leaking from a lateral lenticulostriate artery (arrow).

Case 4

A 12-year-old boy was admitted unconscious after a road accident. He was hypotensive with right sided spasticity and a fixed dilated right pupil. Later the left pupil became fixed and dilated.

Carotid angiography by direct puncture two hours after admission showed shift of midline structures to the right and a deep avascular mass. Extravasation of contrast medium from one of the lateral lenticulostriate arteries was seen about one second after injection (Fig. 7) and it increased in amount throughout the series of films (Fig. 8). It was still visible on a film taken five minutes later (Fig. 9).

A left temporal burr hole was made and 30 ml of blood clot was aspirated. Blood was seen to spurt from a brain cannula at arterial pressure. It was felt that the haemorrhage could not be controlled without extensive brain dissection, and no further surgery was attempted. The patient died three days later. Autopsy confirmed the presence of a large basal ganglion haematoma which had ruptured into the

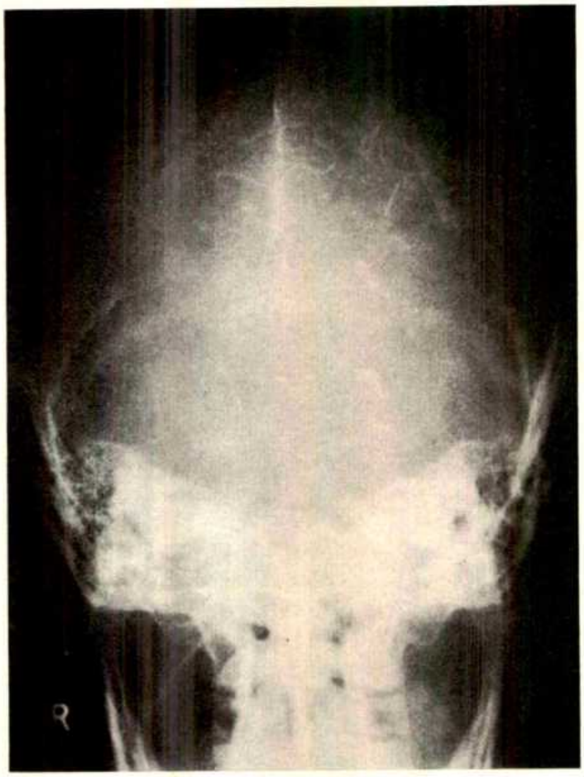


FIG. 8. *Case 4.*

Venous phase of same examination showing a collection of extravasated contrast medium in the basal ganglia.

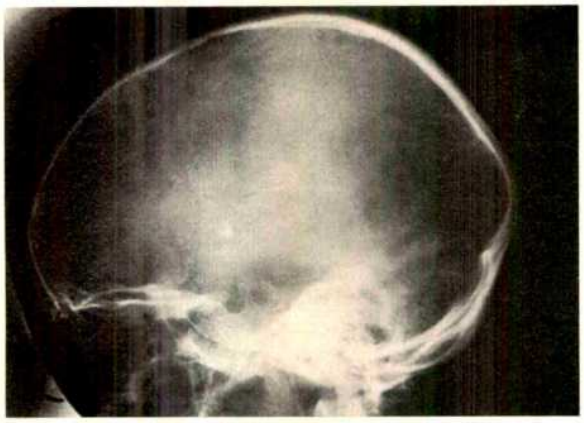


FIG. 9. *Case 4.*

Plain film five minutes later shows persistence of extravasated contrast medium.

lateral ventricle. There was no skull fracture and no aneurysm or angiomatous malformation was seen.

Case 5

A 16-year-old girl was admitted unconscious after a road accident. She was found to have a frontal fracture with brain tissue extruding. She was also bleeding from the right ear suggesting extension of the fracture into the petrous bone. As she had left hemiplegia a right carotid angiogram was performed. This showed an extra-cerebral block of the internal carotid artery, due to thrombosis. Extravasation of contrast medium was noted from meningeal branches of the external carotid artery (Fig. 10).

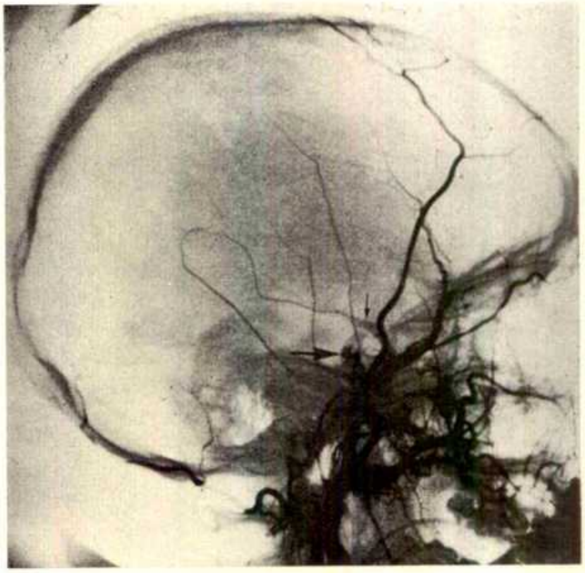


FIG. 10. *Case 5.*

Right carotid angiogram showing extravasation of contrast medium from meningeal arteries in two forms. (1) Amorphous collection in an extradural haematoma (large arrow). (2) "Tram-lines" along the course of a meningeal artery (small arrow) probably due to a traumatic arterio-venous fistula.

She slowly deteriorated and died within 24 hours of injury.

Autopsy showed gross cerebral oedema with severe contusion of the right frontal lobe and contre-coup injuries.

DISCUSSION

Intracranial haemorrhage may follow rupture of an aneurysm or angiomatous malformation. It may be post-traumatic or it may occur "spontaneously", usually in elderly hypertensives. Leakage of contrast medium from intracranial vessels has been demonstrated in all these conditions. Extravasation has not been seen in association with less common causes of intracranial haemorrhage such as cerebral tumours, hypocoagulable states or acute encephalitis.

Aneurysms and angiomatous malformations

Radiological demonstration of aneurysms rupturing during angiography is rare. In the American Co-operative Study (Perret and Nishioka, 1966) 7930 angiograms were carried out on 5484 patients for subarachnoid haemorrhage and extravasation of contrast medium was seen in only one case. We were able to find 43 cases recorded in the literature

LIBRARY

(see Table I). To these we add two cases found in our series of 5184 carotid angiograms.

The infrequency of aneurysmal rupture during angiography suggests that the rupture is usually coincidental to angiography. However, the possibility of angiography contributing to rupture of an aneurysm has been discussed elsewhere (Wright, 1962; Ferrari and Vio, 1969; Vines and Davis, 1971; Waga *et al.*, 1973).

The demonstration of extravasation from an aneurysm was closely followed by death in 34 cases of the 42 in whom the outcome was reported. This represents a mortality rate of 81%. (Two of the survivors had residual haemiplegia.) Demonstration of extravasation from an aneurysm therefore suggests a very poor prognosis.

TABLE I

Extravasation from ruptured aneurysms

Authors	Outcome
1 Jamieson, 1954	Died
2 Jenkinson *et al.*, 1954	Died
3 Gallagher and Yamamoto, 1956	Died
4 Jackson *et al.*, 1960	Died
5 Triska, 1962	Died
6 Pirker, 1964	Not reported
7 Taveras and Wood, 1964	Died
8 Pool and Potts, 1965	Died
9 Roach and Drake, 1965	Died
10 Perret and Nishioka, 1966	Died
11 Goldstein, 1967	Died
12 Murphy and Goldberg, 1967	Died
13 Beamer *et al.*, 1969	Died
14 Ferrari and Vio, 1969	Survived
15 Hoff and Potts, 1969	Died
16 Cerniauskas *et al.*, 1970	Died
17 Freemon, 1970	Died
18 Henry *et al.*, 1971	Died
19 Henry *et al.*, 1971	Survived
20 Palmieri *et al.*, 1971	Died
21 Vines and Davis, 1971	Survived
22 Waga *et al.*, 1973	Died
23 Lehrer *et al.*, 1972	Died
24 Sakamoto *et al.*, 1972	Died
25 Dinning, 1973	Died
26 Karadayi *et al.*, 1973	Died
27 Marc *et al.*, 1973	Died
28 Teal *et al.*, 1973	Died
29 Allcock, 1974	Not reported
30 Allcock, 1974	Not reported
31 Handa *et al.*, 1974	Died
32 Osgood and Martin, 1974	Died
33 Gerlock, 1975	Died
34 Someda *et al.*, 1975	Survived
35 De Tribolet *et al.*, 1976	Survived
36 Lilliequist *et al.*, 1976	Survived
37 Allcock (Wilkins 1976)	Died
38 Beamer (Wilkins 1976)	Died
39 Hurt (Wilkins 1976)	Survived
40 Vander Ark (Wilkins 1976)	Died
41 Vander Ark (Wilkins 1976)	Died
42 Waltz (Wilkins 1976)	Died
43 Wilkins, 1976	Died

Our case of extravasation from an angiomatous malformation (Case 3) is the second such case to be reported. Our patient survived without neurological impairment but death occurred in the other reported case (McLennan *et al.*, 1974).

Trauma

Previous reports suggest that extravasation of contrast medium is quite frequently seen in traumatic rupture of meningeal vessels and extradural haemorrhage (Table II). We have seen one case in this group (Case 5), but the majority of our patients had a selective internal carotid artery injection and the meningeal vessels were not seen.

Kuramoto *et al.* (1969) found a 25% mortality rate in his patients with extradural haemorrhage in whom extravasation was seen. Schechter *et al.* (1966) commented that the size of the extradural haematoma found at surgery was unrelated to the observation of extravasation of contrast at carotid angiography. Therefore, it seems that angiographic demonstration of bleeding is not necessarily associated with a poor prognosis in extradural haemorrhage.

Demonstration of active bleeding from ruptured cerebral, rather than meningeal, vessels following trauma is very uncommon. Only 12 cases are reported in the literature (see Table III). In most of these cases there was a skull fracture with rupture of superficial cerebral arteries. Two cases of deep intracerebral extravasation have been reported

TABLE II

Reported cases of extravasation in subdural and extradural haemorrhage

Authors	Number of cases	Deaths
1 Löhr, 1936	4	2
2 Jamieson, 1952	1	–
3 Lofstrom *et al.*, 1955	1	–
4 Tiwisina and Stäcker, 1959	2	2
5 Vaughan, 1959	1	–
6 Huber, 1962	7	5
7 Cronquist and Köhler, 1963	1	?
8 Wortzman, 1963	4	?
9 Zingesser *et al.*, 1965	4	1
10 Schechter *et al.*, 1966	8	5
11 Ferris *et al.*, 1967	6	?
12 Galligioni *et al.*, 1968	2	–
13 Helmer *et al.*, 1968	1	–
14 Katsurada *et al.*, 1968	4	?
15 Kuramoto *et al.*, 1969	8	2
16 Jamieson, 1972	1	–
17 Saba and King, 1973	1	1
18 Glickman, 1974	1	?
Total	57	18

TABLE III

Post-traumatic extravasation from cerebral arteries

Authors	Outcome
1 Webster *et al.*, 1951	Survived
2 Tiwisina and Stäcker, 1959	Died
3 Tiwisina and Stäcker, 1959	Died
4 Schmidt and Rossi, 1961	Died
5 Schechter *et al.*, 1966	Not reported
6 Rudikoff *et al.*, 1968	Not reported
7 Rudikoff *et al.*, 1968	Not reported
8 Fujino and Hara, 1969	Survived
9 Kodama *et al.*, 1971	Died
10 Ito *et al.*, 1972	Survived
11 Thierry *et al.*, 1973	Died
12 Glickman, 1974	Not reported

following penetrating injury (Kodama *et al.*, 1971 and Thierry *et al.*, 1973). We believe our Case 4 is the first report of deep intracerebral extravasation occurring after non-penetrating head injury. The mechanism of injury to the lenticulostriate arteries in our case is speculative.

The site of the haematoma is similar to that seen in spontaneous intra-cerebral haemorrhage where Russell (1963) and Cole and Yates (1967) have demonstrated micro-aneurysms of the lenticulostriate arteries. However, such micro-aneurysms are rare in normotensive individuals and their incidence is age related. Their occurrence in a 12-year-old-boy is therefore unlikely.

The outcome has been reported in ten of the thirteen cases of extravasation from cerebral arteries following trauma. Six of these patients died and only one of the survivors is stated to have made a complete recovery. Extravasation from cerebral vessels therefore appears to have a serious prognostic significance, perhaps because it usually reflects more severe trauma than meningeal artery rupture.

Hypertensive intracerebral haemorrhage

Yamaguchi *et al.* (1971) have suggested that when carotid angiography is undertaken soon after spontaneous cerebral haemorrhage, extravasation is seen quite frequently. They found extravasation in five patients in 44 cases that they studied. This incidence of 12% is supported by Huckman *et al.* (1970).

We found no definite cases of extravasation in this group but we could trace few patients who had had angiography and had intracerebral spontaneous haemorrhage confirmed at surgery or post mortem. We had one case who had undoubted extravasation and who probably had a hypertensive bleed. We have not recorded this case in detail for autopsy was not carried out and there was a suggestion of an angiomatous malformation on an unsatisfactory angiogram.

Our series probably contained many unconfirmed cases of spontaneous intracranial haemorrhage. However, the small number of cases which we could trace probably reflects the relatively conservative management of this condition in Oxford.

It is difficult to estimate the prognostic significance of extravasation in this group from our data or from that available in the literature.

Conclusion

Extravasation of contrast medium at carotid angiography is rare. It is associated with a poor prognosis in bleeding cerebral aneurysms and post-traumatic rupture of cerebral arteries. It does not necessarily imply a poor prognosis in extradural haemorrhage. Its prognostic significance is uncertain in hypertensive cerebral haemorrhage and in ruptured cerebral angiomatous malformation.

Acknowledgments

We wish to thank Mr. C. Adams and Mr. M. Briggs, Consultant Neurosurgeons, for permission to publish these cases, and to Dr. P. W. E. Sheldon, Consultant Radiologist, for his advice. We are indebted to several friends and colleagues for translations and to the secretarial staff of the Radcliffe Infirmary X-ray Department for much typing.

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Book review

Special Procedures in Chest Radiology. Edited by Stuart S. Sagel, pp. 219, 137 illus., 1976 (W. B. Saunders Company), £12·95.

This book is No. 8 of the series of the Saunders *Monographs in Clinical Radiology*, and deals with some of the special procedures used in the modern practice of chest radiology. It has been well written by the seven contributors, well known experts in this field in the U.S.A. They have described the techniques of the procedures which they employ, with some valuable hints, which any radiologist about to embark on one of these will find of great help.

Alternate methods are only briefly mentioned. For example, in the chapter on bronchography, only the cricothyroid route is described. Nor should the reader expect a full discourse on all the special procedures which can be used in chest radiology. Notable omissions are perhaps venography, and barium studies of the oesophagus in mediastinal disease.

Nevertheless, the authors have stressed the very real change in attitude to radiological diagnosis in diseases of the chest which has taken place over the past few years. A conclusive tissue or bacteriological diagnosis which may be obtained by a fluoroscopically assisted biopsy technique is far more valuable than multiple plane tomography, bronchography or pulmonary arteriography in many instances. A logical approach is thus made to the indications for the various procedures, and it is this which makes the book a valuable contribution to the practice of clinical radiology.

In addition to chapters on tomography, bronchography, pulmonary arteriography, aortography biopsy techniques and paediatric pulmonary techniques, there is an excellent chapter on nuclear medicine in lung disease by Dr. Secker-Walker. This contains a concise description and critical assessment of the various techniques in chest disease which employ radio-active isotopes, and can be easily assimilated by radiologists not specializing in nuclear medicine.

This book is highly recommended for all radiologists for, as Dr. Potchen says in the Foreword, "Chest X-ray interpretation represents some 35% of the practice of diagnostic radiology".

I. H. KERR.

1977, *British Journal of Radiology*, *50*, 412–414

The radiology of nasal injuries: problems of interpretation and clinical relevance

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ABSTRACT

Films of 50 normal patients and 50 dry skulls were examined to detect lines which might simulate a nasal fracture. These were visible on the occipito-mental view but on the lateral view any line which reaches the anterior cortex must be regarded as a fracture. The results of an analysis of 100 patients with trauma to the nasal bone are also presented. It is concluded that radiography of the nasal bone is an unnecessary examination unless requested by the E.N.T. surgeon, and this will in any case occur infrequently.

It is common practice for patients attending the Accident Department following nasal trauma to be sent for X-ray examination. The reasons given are that this may aid clinical management, that there is a medico-legal consideration, and that a normal finding will provide patient reassurance. It was to determine the value of radiography in nasal trauma that this study was performed.

MATERIALS AND METHODS

The films and notes of 100 consecutive patients attending the Accident Department at St. George's Hospital with a history of trauma to the nose were evaluated. In each case the history and physical examination were recorded, the films re-examined and clinical management documented. In addition the occipito-mental views (Waters) of 50 patients attending without trauma were examined, and the position of any defects in the nasal bone noted. The lateral view of the skulls of the same patients were too over-exposed for evaluation of the nasal bone, and a non-screen film was therefore attached to the outside of the cassette used for 50 patients attending for routine skull films. Finally, 50 dry skulls were radiographed in the occipito-mental projection, and when nasal bone defects were seen the skull was scrutinized to explain the finding.

DISCUSSION

The routine views of the nasal bone at St. George's Hospital are a lateral and occipito-mental (Waters). Early in this study two problems became apparent. Firstly, short lucent lines reaching the anterior aspect of the nasal bone were being interpreted as normal because of the absence of a step in the cortex. To determine whether such lines could be a normal finding the lateral view of 50 normal nasal bones were scrutinized, but none were found. Thus, any line reaching the anterior wall of the nasal bone, should be regarded as a fracture.

Secondly, on the occipito-mental view of the patients with nasal injury, defects in the bone were seen but seemed unlikely to represent fractures. The occipito-mental view of the 50 normal patients confirmed this impression: 13/50 showed mid-line defects (Fig. 1A), 12/50 high lateral wall defects (Fig. 1A) and 8/50 showed low lateral wall defects (Fig. 1B). Comparison with the films of dry skulls showed that these defects were due to the mid-line nasal suture, the naso-maxillary suture (low defect) and a developmental defect or thinning of the nasal wall (high defect). This incidence of 33 cortical defects in 50 normal patients makes assessment of nasal fractures on this view unreliable. The incidence of fractures, the views on which they were seen, and the management of the patients with nasal injury are shown in Table I.

In this series 45 of the 100 patients had fractures of the nasal bone but only three required reduction of the fracture. In each case the reduction was indi-

TABLE I

100 PATIENTS WITH NASAL TRAUMA REFERRED FOR X-RAY EXAMINATION

No X-ray evidence of a fracture		65
Number with a fracture of the nasal bone		45
View on which fracture seen	Lateral only	41
	Occipito-mental only	2
	Lateral and occipito-mental	2
Management of patients with a fracture	Discharged without treatment	31
	Referred to E.N.T. Clinic	14
Management of patients referred to E.N.T. Clinic	Did not attend	5
	Discharged without treatment	6
	Admitted for reduction	3

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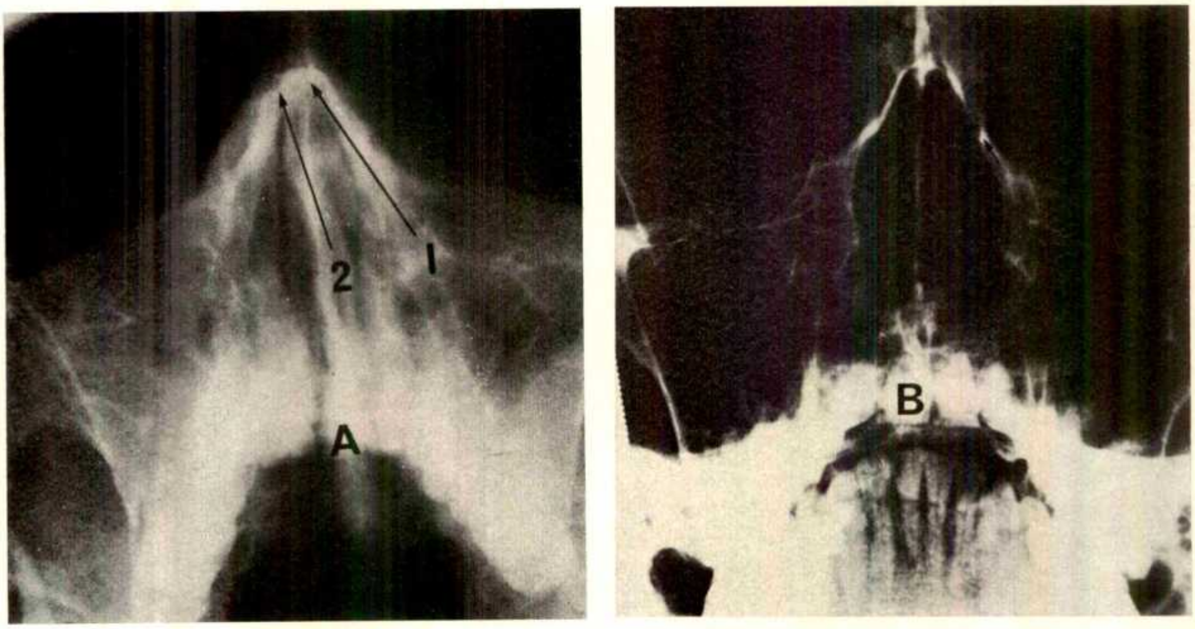
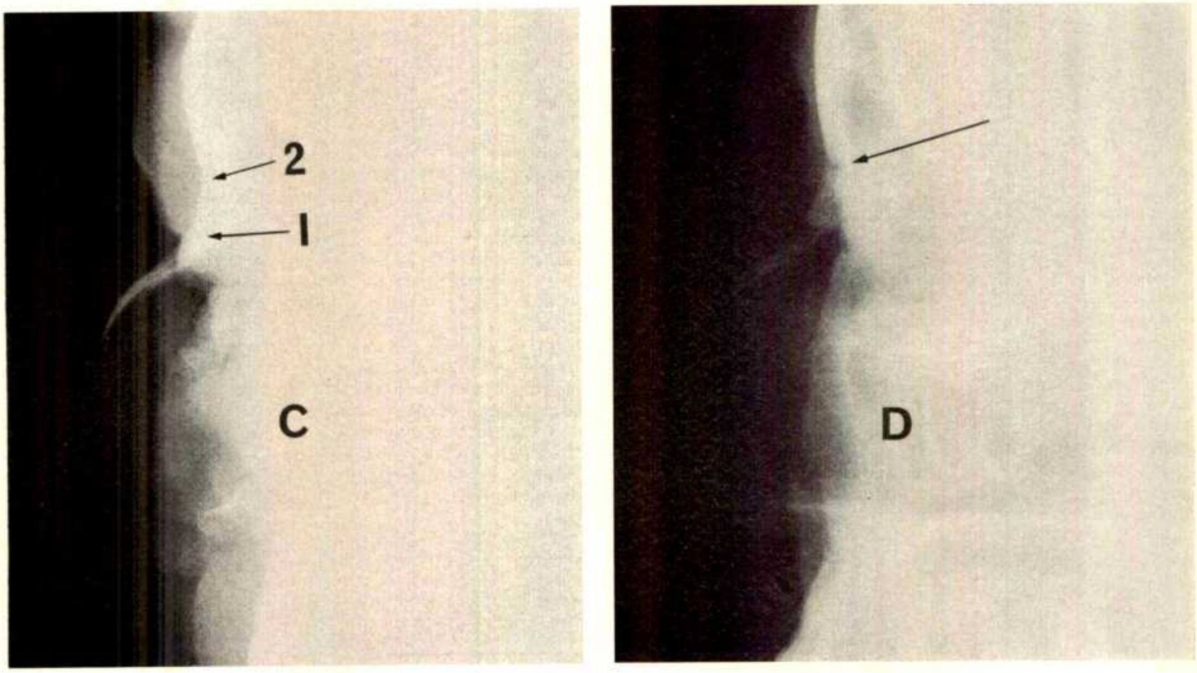
FIG. 1.



A B

(A) Occipito-mental view of normal nasal bone showing a mid-line defect (1) and a high lateral wall defect (2).

(B) Occipito-mental view of normal dry skull showing a low lateral wall defect.



C D

(C) The lucent line (1) reaching the anterior cortex is a fracture and should not be confused with the naso-frontal suture whose position is indicated by (2).

(D) Normal nasal bone showing position of naso-frontal suture.

cated because of a clinical deformity and not because of the X-ray appearance. The X-ray examination did not contribute to clinical management in any case. It has been emphasized (Hughes, 1974; Facer, 1975) that a septal haematoma requires careful clinical management and this important injury may be ignored because too much reliance is placed on the X-ray demonstration of a normal or fractured nasal bone. Of course, if the blow to the nose may have clinically involved other facial bones, such as the inferior wall of the orbit, then the appropriate facial views should be obtained; but views of the nasal bone itself are totally unnecessary. The medico-legal connotation undoubtedly does influence some casualty officers and thus unnecessary X rays may be requested. It requires stating emphatically that there is no medico-legal reason for taking X rays of the nasal bone, as treatment of a fracture will depend solely on the functional or cosmetic effect and this depends only on the clinical findings. Patient reassurance should be based on good clinical examination and not on wasteful radiography. The results of this study represent an example of radiography which is of no clinical value (Reidy *et al.*, 1975; Bull and Zilkha, 1968; de Lacey, 1976). Radiography of the nasal bone is not indicated in the Accident Department, and films should only be obtained if requested by the E.N.T. surgeon.

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Book review

Speak To Me In Nuclear Medicine. By Phillip Shtasel, pp. xvi+223, illus., 1976 (Hagerstown, Maryland, U.S.A., Harper and Rowe Inc.) $22.50.

What, another book on nuclear medicine! But this one is different—quite a lot different in style and layout though not so very different in content.

Speak To Me In Nuclear Medicine engagingly confesses that the last thing the world needs is another text on nuclear medicine but this chatty, colloquial book is aimed at general physicians, a field which the author feels is not covered by other texts. Technical aspects of the subject are therefore excluded and chapters are organized under headings of "what", "why" and "how" embellished with "cute" drawings and art magazine text layout. The effect is refreshing but at times confusing. What is "what"? (It is, in fact, the choice of radiopharmaceutical available for any particular examination.) Metaphors at times become difficult for the mere European; "Wow The situation was analogous to the ace of the pitching staff walking the end of the batting order with none out. A hurry-up call went out to the bull pen. Enter Mr Nuclear Medicine". After sorting through the unusual wrapping there is, however, a lot of substance in this fairly small volume and the data is presented with many clinical examples and a balanced view of the advantages and disadvantages of radioisotope scanning in comparison with other alternatives. The illustrations are marred (in my view) by the use of polaroids. If polaroid film has to be used due to the lack of film processor (and why a department of nuclear medicine in the U.S.A. should lack such a thing is mysterious) would it not be a good idea to reverse pictures so that they match the linear scans?

I can recommend this book for what it sets out to do, that is, to give a reasonably up-to-date short text on radioisotope organ imaging untrammelled by computers or compartments.

D. R. LAVENDER.

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Thrombogenicity of arterial catheters and guidewires

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ABSTRACT

Thrombus formation on the surface of a variety of arterial catheters and guidewires has been studied in dogs. Heparin-bonding of catheters and guidewires greatly reduced surface thrombus deposition even in the most thrombogenic material tested, and under the conditions of these experiments heparin-bonding was more effective than systemic heparinization.

Diagnostic radiologists are increasingly performing arterial catheterization procedures in peripheral and visceral vascular disease. Arterial catheters may remain in the arterial system for long periods, particularly when used for therapeutic perfusion techniques in malignant diseases.

It is known that thromboembolism following cardiac and visceral catheterization can have serious consequences (McCarty and Glasser, 1973), but the recorded incidence of thromboembolism of clinical importance is low, bearing in mind the high incidence of thrombus deposition on catheter materials recorded both clinically and experimentally (Jacobsson *et al.*, 1969; Formanek *et al.*, 1970).

Some plastic materials are more thrombogenic than others (Formanek *et al.*, 1970; Ovitt *et al.*, 1974), but their thrombogenicity may be reduced either by systemic heparinization or by coating the surface of these materials with heparin (Anderson *et al.*, 1974).

In this paper we have attempted to quantitate in comparative terms the thrombogenicity of different catheters and guidewires and the effect of heparin-bonding on the relative thrombogenicity of these materials.

MATERIALS AND METHODS

A total number of 104 catheters and guidewires of various types were tested in four mongrel dogs weighing between 12 and 22 kg. In each dog both femoral arteries were cannulated, enabling synchronous testing of heparinized and untreated catheters and guidewires in the same animal. The cannula was designed to allow introduction and withdrawal of the test materials without the risk of disturbing or removing any thrombus from their surface (Fig. 1). Four centimetres of each guidewire or catheter protruded beyond the tip of the introducer, which in turn was passed through the indwelling cannula.

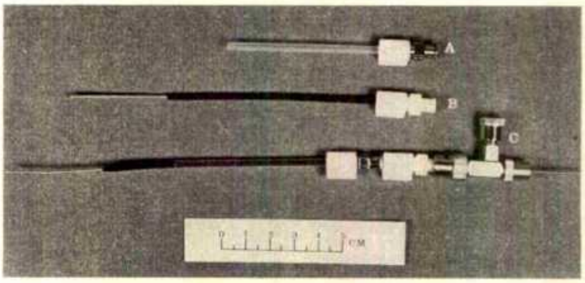


FIG. 1.

Device for introducing test materials into the femoral artery. A is the indwelling cannula. In B and C a catheter and guidewire are mounted in Teflon sheaths, which in turn are introduced into the artery through the cannula A.

Uncoagulated blood was removed from the surface of the catheters and guidewires by gently rinsing in saline, and the amount of thrombus deposited was assessed by examination under a low-power dissecting microscope and also by scanning electron microscopy (SEM). The thrombus deposited on the surface of the guidewires was weighed following its removal from the surface by withdrawing through a tight-fitting catheter. The catheters examined by SEM were fixed with 2% cacodylate-buffered glutaraldehyde immediately after withdrawal from the artery.

The fourth dog in this study was systemically heparinized with 45 units of heparin/kg body weight, followed by 3 to 5 ml of a 1000 unit/500 ml normal saline dilution every two to three minutes throughout the procedure.

The whole-blood clotting-time (WBCT) in the four dogs varied between one and three minutes, but was constant in each animal. The WBCT remained unaffected by the procedures performed. For systemic heparinization in the fourth dog, the WBCT was maintained at three times the normal for this animal.

The guidewires tested were stainless steel round-wound (Cook, Type SF35.30), Teflon-coated stainless steel (Cook, Type TSF35.30), flat polished ribbon (Cook) and green polyethylene with core (Cook). The catheters tested were red polyethylene (Cook, Type 5.0), and green polyethylene (Cook, Type 7.2).

Results

Guidewires were more thrombogenic than the catheters for a given time of exposure in arterial blood, except for the polyethylene guidewires, which were the least thrombogenic of all the non-heparinized materials used. Teflon-coated guidewires were considerably more thrombogenic than stainless steel guidewires. For the purposes of comparison, the weight of thrombus removed for each 4 cm length of exposed material has been expressed in units rather than mg (Table I). The stainless steel flat polished ribbon guidewires were less thrombogenic than the roundwound type.

The amount of thrombus deposited on the surface of the catheters depended on the duration of exposure to arterial blood, but the green catheters were more thrombogenic than the red catheters (Table II).

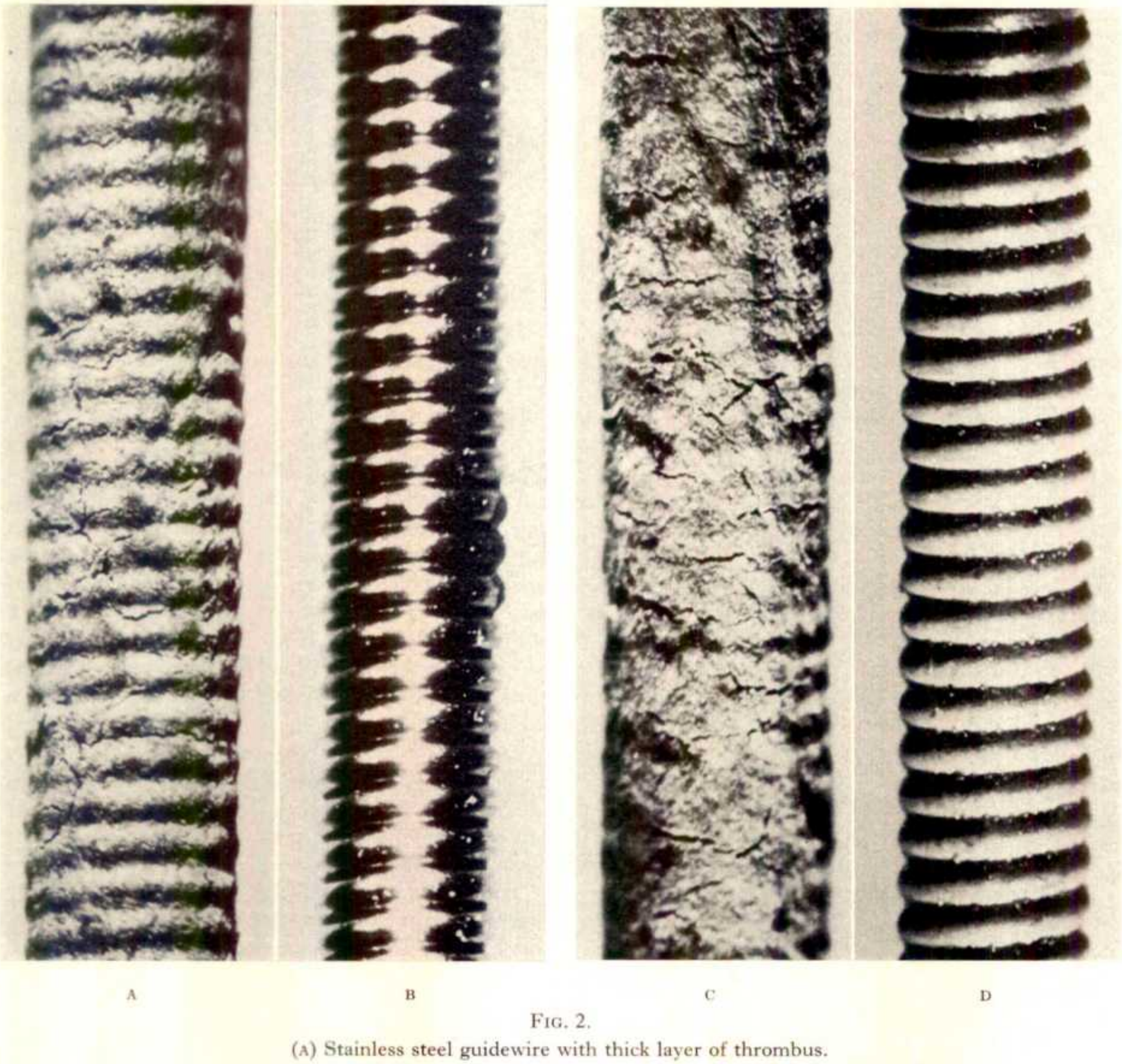


Fig. 2.

(A) Stainless steel guidewire with thick layer of thrombus.

(B) Heparinized stainless steel guidewire.

(C) Teflon-coated guidewire with thick layer of thrombus.

(D) Heparinized Teflon-coated guidewire with minute deposits of thrombus in the windings of the wire. In each case the guidewire was exposed to arterial blood for 10 min.

In the early stages of deposition, the thrombus consisted of fibrin strands, but later it consisted of a thick layer of red blood cells enmeshed in fibrin (Fig. 3).

Heparin-bonded catheters and stainless steel guidewires were free of thrombus, and only minute amounts of thrombus formed on the heparin-bonded Teflon-coated guidewires (Figs. 2 and 3).

Under the conditions of these experiments, heparin-bonding of the stainless steel guidewires was more effective at inhibiting thrombus deposition than systemic heparinization (Table I).

TABLE I

GUIDEWIRES

Type	Heparin bonding	Thrombus deposition	
		Thrombus weight	Low power microscopy*
Stainless steel	0	25–50 units	++
	+	1 unit	0
	S.H.	3 units	+
Teflon-coated	0	100 units	+++
	+	1 unit	0–+
Flat polished ribbon	0	30 units	+ (patchy)
Poly-ethylene	0	0	0
	+	0	0

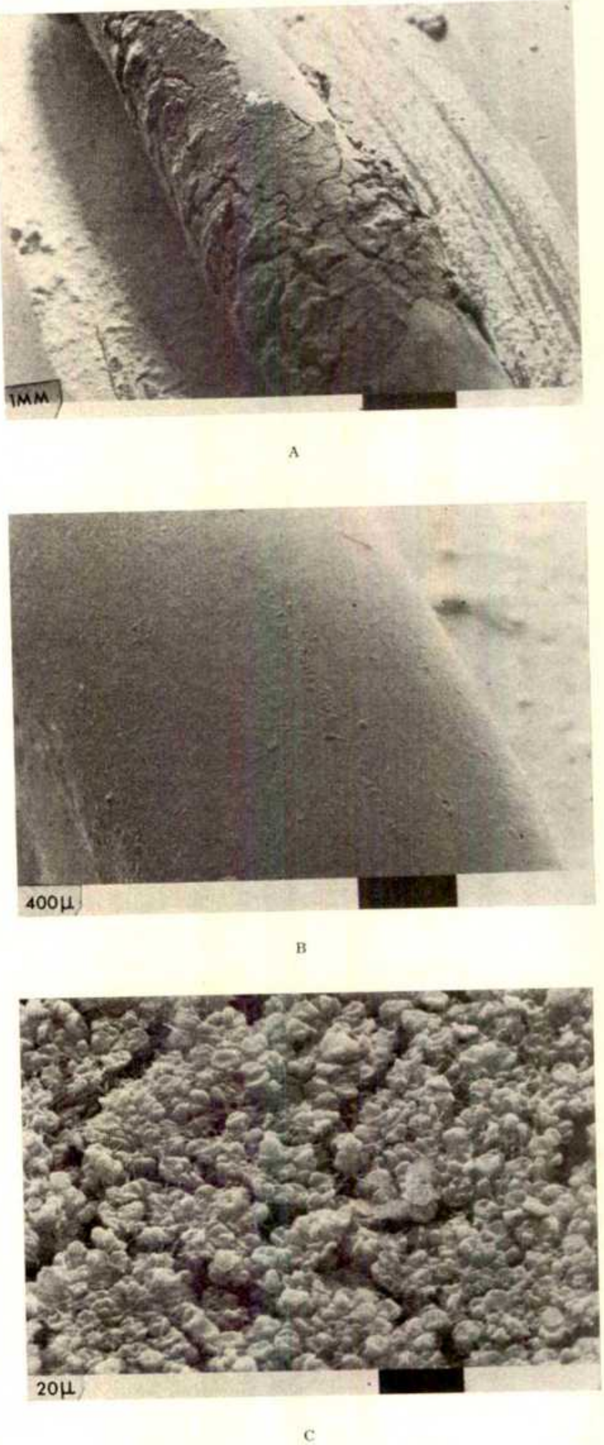
S.H. = Systemic Heparinization.
*(+++ large amount of thrombus; ++ moderate; + little; 0 nil).

TABLE II

CATHETERS

Type	Heparin bonded	Exposure time	Thrombus deposition	
			Low power microscopy*	S.E.M.*
Red	0	10 min	0–+	+
	+		0	0
	0	30 min.	+	++
	+		0	0
Green	0	10 min.	+	++

*(+++ large amount of thrombus; ++ moderate; + little; 0 nil).



A

B

C

FIG. 3.

Red Cook catheter after 30 min exposure to arterial blood.

(A) Untreated.

(B) Heparinized.

Note meshwork of fibrin and red cells in (C).

Discussion

The results of these experiments confirm the findings of others *viz.* that Teflon is intensely thrombogenic (Formanek *et al.*, 1970; McCarty and Glasser, 1973; Ovitt *et al.*, 1974) and that heparinization of the guidewires and catheters reduces and may abolish thrombus deposition (Anderson *et al.*, 1974; Ovitt *et al.*, 1974). Our results indicate that polyethylene guidewires are the least thrombogenic of the guidewires tested, and that the same low degree of thrombogenicity can be achieved in more susceptible materials by heparin-bonding.

In clinical practice long guidewires and catheters may remain in the arterial system for longer periods of time than those used in these experiments. It has been shown that thrombus deposited on the surface of guidewires and catheters may be stripped off during withdrawal of the catheter from the artery (Frech *et al.*, 1971; Eldh and Jacobsson, 1974). This may predispose to local thrombosis of the vessel and to peripheral embolization (Formanek *et al.*, 1970). Eldh and Jacobsson (1974) have suggested that a disadvantage of using heparin-bonded catheters appears to be a prolongation of compression time over the puncture site to establish haemostasis, particularly with polyethylene catheters.

The inhibition of thrombus formation on the heparin-bonded catheters shown in this work might explain the lower incidence of thromboembolism and arterial thrombosis recorded by Cramer *et al.* (1973).

The relevance of our findings to the clinical situation, *i.e.* the investigation of patients by arteriography, is difficult to assess in view of the relatively low incidence of complications. The increased cost of heparinized materials also has to be taken into consideration.

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The combined use of iron 52 and its contaminant iron 55 in studies of the bone marrow

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ABSTRACT

A liquid scintillation counting technique has been used to measure ^{55}Fe incorporation into red blood cells with counting efficiencies of the order of 10% for 0.1 ml whole blood. Measurements have been carried out over a period of two weeks following the intravenous administration of the short-lived cyclotron produced ^{52}Fe which contains ^{55}Fe (half-life 2.6 years) as contaminant.

^{52}Fe, with its short half-life of 8.2 hours and suitable γ-ray emissions, is the isotope of choice for bone marrow imaging and short term ferrokinetic studies such as plasma clearance and early organ uptake of iron. However, long term iron utilization cannot be measured with this radionuclide alone. By exploiting the presence of ^{55}Fe this limitation has now been overcome.

In assessing erythropoietic function, traditional ferrokinetic studies with ^{59}Fe are used in order to determine the rate of plasma iron clearance and turnover in the first few hours and iron utilization expressed as a percentage of the administered dose incorporated into circulating erythrocytes over a period of ten to 14 days. The latter measurement provides information on the ultimate effectiveness of erythropoiesis and, taken in conjunction with plasma iron clearance, will often distinguish between the reduced erythropoiesis of marrow hypoplasia and the defective erythropoiesis of marrow dysplasia or dyserythropoiesis.

Surface counting is an ancillary procedure for determining the distribution of ^{59}Fe within the body. However, its value is limited as the small segment of bone marrow "seen" by the collimated counters is not necessarily representative of the skeleton as a whole and it is not possible to obtain a quantitative measurement of the extent of iron uptake in various organs.

^{52}Fe is a short-lived cyclotron-produced radionuclide of iron used for bone marrow imaging (Anger and Van Dyke, 1964; Van Dyke and Anger, 1965; Van Dyke *et al.*, 1967). ^{52}Fe can also be used for quantitation of organ uptake of iron in a short-term study, thus providing valuable information which cannot be obtained by ^{59}Fe surface counting (Bruce-Tagoe *et al.*, 1973; Pettit *et al.*, 1976). With ^{52}Fe it is also possible to measure plasma iron clearance but the disadvantage of ^{52}Fe is that its short half-life of 8.2 hours precludes long term study of iron utilization. Moreover, the dose of ^{52}Fe which can be administered is limited by the presence of ^{55}Fe (half-life 2.6 years) as a contaminant. The work described in this paper was undertaken in order to determine whether the presence of ^{55}Fe might be used to overcome the limitation of studies with ^{52}Fe; a liquid scintillation counting technique for measurement of ^{55}Fe utilization is described.

MATERIALS AND METHODS

Patients studied

Investigations with ^{55}Fe have been carried out on patients randomly selected from those referred to the haematology department for ferrokinetic studies with ^{52}Fe. Some of these patients were suffering primarily from haematological disorders and others were studied during a course of radiotherapy for non-haematological malignancies. Haematological data at the beginning of each investigation are shown in Table I. Relevant treatment during the course of each ferrokinetic study together with the final diagnosis are also given.

Radionuclide

^{52}Fe is prepared by the M.R.C. Cyclotron Unit by bombarding natural chromium with 30 MeV alpha particles (Thakur *et al.*, 1971). ^{52}Fe emits 511 keV positrons and 170 keV γ rays and has a half-life of 8.2 hours. Its physical characteristics have been described in detail elsewhere (Francois and Szur, 1958). The dose of ^{52}Fe which can be administered is limited by the presence of ^{55}Fe as contaminant produced by ^{52}Cr (α,n) and ^{53}Cr (α,2n) reactions. Thakur *et al.* (1971) estimated the contamination to be 14% at end of bombardment (EOB), but more recent estimates are as high as 28.6% at EOB (Waters, 1976). The Isotope Advisory Panel of the United Kingdom Department of Health and Social Security, aware of the high level of contamination, recommend that the maximum dose of ^{52}Fe ad-

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TABLE I

CLINICAL AND HAEMATOLOGICAL DATA

Patient	Sex/Age	Final diagnosis and relevant treatment	Hb g/dl.	PCV	WBC $\times 10^9$/l.	Neutrophils $\times 10^9$/l.	Platelet count $\times 10^9$/l.	Serum* iron μmol/l.
W.B.	M/50	Dyshaemopoietic anaemia	8.1	0.281	14.0	7.0	59	15.5
H.H.	M/23	Seminoma testis D.X.R. inverted Y	13.5	0.401	7.5	5.2	380	24.7
A.C.	M/65	Ca. bronchus D.X.R.	11.4	0.357	9.3	4.5	490	6.4
K.R.	M/53	Refractory anaemia	8.5	0.262	2.3	0.9	23	53.7
J.B.	F/49	C.G.L.† Busulphan	6.4	0.203	16.2	7.8	255	—
Y.J.	M/54	Aplastic anaemia	9.7	0.291	4.6	1.5	35	21.9
J.Br.	M/57	C.G.L.† Busulphan	10.8	0.386	19.2	86.4	400	16.3
C.S.	M/69	Myelofibrosis	6.9	0.190	2.1	0.9	68	—
M.C.	M/40	C.G.L.† Busulphan	12.0	0.363	27.5	—	97	22.9

* Normal value for this laboratory is about 20 μmol/l.

† Chronic granulocytic leukaemia.

ministered to adult, non-pregnant patients should be 200 μCi, this containing about 74 μCi ^{55}Fe at the time of administration (three hours after EOB). Calculations of absorbed dose for ^{52}Fe and ^{55}Fe have been made by Lillicrap (Lillicrap *et al.*, 1976). His calculations, based on the ICRP "reference man", the MIRD pamphlets and a biological half-life for ^{55}Fe of 600 days, give the following absorbed doses in mrad/μCi administered intravenously: total body 1.0 (^{52}Fe) and 4 (^{55}Fe), bone marrow 22 and 16, blood 1 and 45, spleen 1 and 25, liver (assuming normal marrow function) 4 and 14, liver (assuming no marrow function) 24 and 90. These figures allow the total dose to be calculated from the time of administration after EOB, the initial proportion of ^{55}Fe contaminant and the actual activity of ^{52}Fe administered.

^{55}Fe has a half-life of 2.6 years and emits a K-capture X ray of 6 keV (Lederer *et al.*, 1967). Long-term ferrokinetic studies, such as incorporation of radio-iron into erythrocytes, are therefore possible.

Clinical methods

Ferrokinetic studies with ^{52}Fe were carried out as described by Bruce-Tagoe *et al.* (1973). Typically 200 μCi ^{52}Fe in the form of ferric citrate was injected intravenously. Blood samples were taken for subsequent measurement of plasma iron clearance. Whole-body bone marrow scans were obtained about three hours* after injection using an Ohio Nuclear Model 84 whole-body scanner. In addition, quantitative scans of liver and spleen were carried out using a Picker Dual Magna-scanner 111 (Pettit *et al.*, 1976). In all cases blood samples were obtained for the estimation of ^{55}Fe incorporation into red cells about the tenth day after administration of the radio-iron, this being the time at which maximum utilization of iron can be expected. Where possible more frequent blood samples were obtained over a period of two weeks.

Plasma clearance

Clearance of ^{52}Fe from plasma was measured in a NaI(Tl) well-type scintillation counter. Blood samples were allowed to stand for at least one hour before separation of the plasma to allow equilibration between ^{52}Fe and its daughter ^{52}Mn^{m}. Plasma clearance of ^{55}Fe was found by counting 1 ml. of plasma in 9 ml Instagel† in a Packard Tri-carb Liquid Scintillation Spectrometer. The plasma clearance half-time for each radionuclide was found from a least squares fit of net plasma counts as a function of time after injection.

Preparation of whole blood for ^{55}Fe utilization

The preparation of whole blood requires a somewhat lengthy procedure which results in a clear sample with counting efficiencies of about 10% for 0.1 ml whole blood. The solutions required are:

(1) Soluene-350‡ (0.5N quaternary ammonium hydroxide in toluene) and Isopropanol mixed in the ratio 1:1.

(2) Instagel and 0.5N hydrochloric acid mixed in the ratio 9:1.

(3) 35% hydrogen peroxide.

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* In a preliminary study measurements at three hours and 20 hours were compared; as there were no significant differences between results at these times, for the present study measurements were taken at three hours only.

† Packard Instrument Company Limited.

‡ Packard Instrument Company Limited.

0.1 ml of whole blood was mixed in a glass counting vial with 1.5 ml of the Soluene–Isopropanol mixture with gentle agitation to lyse the red cells. 0.5 ml of hydrogen peroxide was added with occasional swirling to decolorize the blood. The vial was capped loosely to avoid loss of volatile radioactive products and the samples left to stand at room temperature for about one hour. Fifteen ml of the Instagel mixture was then added and the vial capped and shaken vigorously. After light and temperature stabilization for at least two hours, the samples were counted in a Packard Tri-carb Liquid Scintillation Spectrometer.

The blood samples were prepared for counting as soon after collection as possible. The haematocrit was determined for each specimen and about five samples were prepared for each assay. 0.1 ml aliquots of plasma were prepared for counting in the same way, thus ensuring the same chemical composition and volume. A known fraction of the administered radioactivity was retained as a standard for each patient studied and 0.1 ml aliquots were prepared for counting as above. A pre-dose blood sample was used to provide background count-rates for whole blood and plasma.

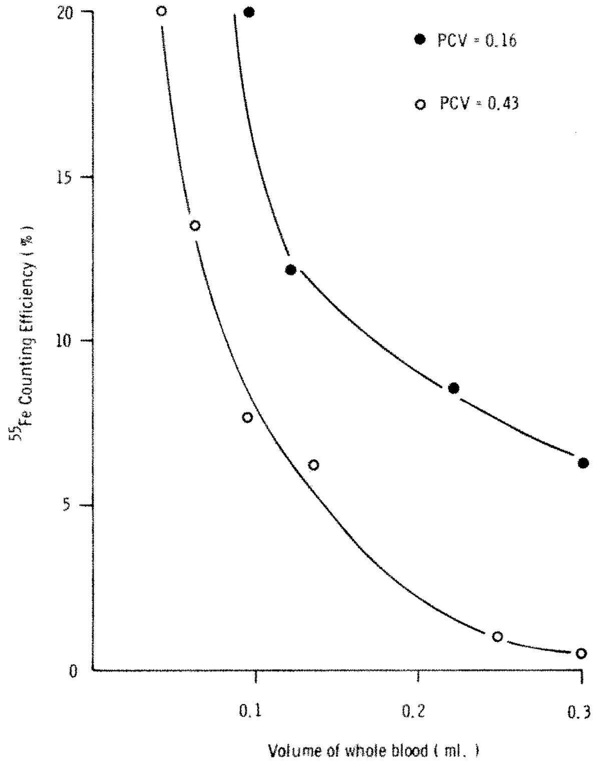

FIG. 1.

Counting efficiency of ^{55}Fe plotted as a function of volume of whole blood incorporated into liquid scintillator for patients J.B. (PCV=0.43, post transfusion) and C.S. (PCV=0.16). Blood samples collected seven days after administration of radio-iron.

Colour quenching

The addition of a highly coloured material such as whole blood to a liquid scintillator causes a great diminution in the scintillation efficiency. Colour quenching has been reduced by counting the minimum amount of specimen which can be dispensed accurately and by bleaching the blood with hydrogen peroxide before incorporation into the scintillator.

In order to investigate the variation of colour quenching with the volume of whole blood, volumes of 40 μl up to 300 μl of a given blood sample were prepared for counting as described above. The actual amount of whole blood was determined by weighing. After counting the samples, 20 μl of a non-quenching standard of ^{55}Fe was added to each vial and the samples recounted. Figure 1 shows the counting efficiencies obtained for different volumes of whole blood. Results for a patient with near normal haematocrit are compared with those for a patient with a very low haematocrit. For the present work the most convenient volume was found to be 0.1 ml, giving count-rates of the order of 200 counts per minute with a background count-rate of 60 counts per minute. Long counting times (100 minutes) were used.

An internal standard of ^{55}Fe was used to correct for colour quenching for all blood samples when estimating utilization.

RESULTS

Table II shows the results of the ^{52}Fe study for each patient together with half-disappearance time of activity from the plasma ($T_{\frac{1}{2}}$) and erythrocyte utilization as a per cent of injected ^{55}Fe activity, measured by liquid scintillation counting. Where serial blood samples were available additional information on iron utilization was obtained (such as Fig. 2).

DISCUSSION

Results for plasma clearance measured by counting both ^{52}Fe and ^{55}Fe are in good agreement. It has thus been possible to use plasma clearance of ^{55}Fe to demonstrate that ^{52}Fe and ^{55}Fe appear to behave in an identical manner, at least in the early phase of the iron pathway.

The ^{55}Fe utilization measurements are consistent with findings which were expected from the haematological status and clinical diagnosis in each case and correlated with organ uptake of iron, that is decreased skeletal uptake or dyserythropoiesis was associated with markedly reduced red cell utilization

TABLE II

Results of combined ^{52}Fe and ^{55}Fe ferrokinetic studies

Patient	T$_{\frac{1}{2}}$ plasma clearance* (min)		3 h uptake of ^{52}Fe as per cent of injected dose		Skeletal uptake of ^{52}Fe on 3 h whole body scan	Red cell utilization of ^{55}Fe as per cent of injected dose
	^{52}Fe	^{55}Fe	Spleen (<1%)†	Liver (<5%)†		
W.B.	16	18	3	5	increased uptake	25% at day 11
H.H.	138	—	1	18	decreased uptake especially over lower part of skeleton	
A.C.	48	49	<1	3	normal uptake	45% at day 12
K.R.	180	184	<1	14	decreased uptake	57% at day 14
J.B.	22	23	20	13	decreased uptake	37% at day 6
Y.J.	153	194	4	13	decreased uptake	26% at day 6
J.Br.	70	75	12	8	decreased uptake	24% at day 15
C.S.	121	117	5	13	decreased uptake	29% at day 7
M.C.	70	71	4	12	decreased uptake	35% at day 8
						34% at day 6

* Normal 60–120 minutes.

† Limits of normal ^{52}Fe uptake found at this hospital.

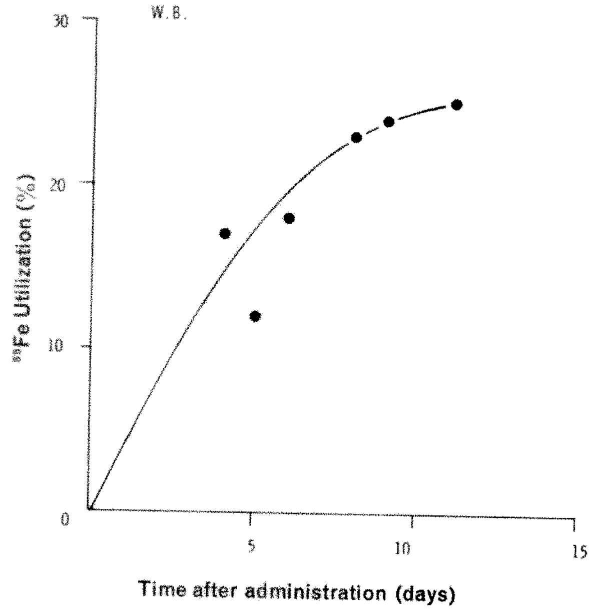

Fig. 2.

Red cell utilization as per cent of injected ^{55}Fe activity for patient W.B.

(normal ±80% at day 10).

It is well established that measurements with ^{52}Fe give more accurate quantitative data on ferrokinetics in the first 24 hours than traditional studies with ^{59}Fe. By measuring the ^{55}Fe activity which is present as a contaminant of the cyclotron produced ^{52}Fe, it is possible to extend the ^{52}Fe study and obtain data on red cell utilization of radio-iron, thus enabling a long-term study to be carried out with a single injection of ^{52}Fe. This procedure therefore overcomes the limitations to the use of ^{52}Fe in ferrokinetic studies which has hitherto required a combined study with ^{52}Fe and ^{59}Fe.

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Fast neutron effects on multicell spheroids*

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ABSTRACT

Accumulation and repair of neutron damage was measured using multicell spheroids irradiated with neutrons at the Hammersmith Cyclotron. A relative biological effectiveness (RBE) of about 1.5 (ratio of D_0 values) was found for aerobic single cells or small spheroids. Small spheroids accumulated more sublethal neutron damage than single cells, as indicated by a wider shoulder on the survival curve. However, neither single cells nor spheroids repaired sublethal damage when two doses of neutrons were separated by six hours or less. A "therapeutic gain" was observed for larger spheroids containing hypoxic cells, due to an increased RBE of fast neutrons for hypoxic cells amounting to about a factor of two.

The potential value of high-LET radiation for the treatment of human neoplasms has been emphasized in recent years (for reviews, see Broerse and Barendsen, 1973; Elkind, 1970; Field, 1976; Hall, 1973; and Withers, 1973), with the result that some centres now have fast neutrons available for therapy. Use of high-LET radiation is generally rationalized on two premises. First, densely ionizing particles, for which the oxygen effect is reduced, would be advantageous whenever hypoxic cells in human tumours limit the success of radiotherapy with X or gamma rays (Field, 1976; Field *et al.*, 1968; Hall, 1973; Withers, 1973). Second, multifraction experiments with a number of normal tissues and tumour systems in rodents have suggested that neutron RBE may, in some cases, be greater for malignant tissue than for normal tissue (Broerse and Barendsen, 1973; Field, 1976; Hornsey and Silini, 1962), perhaps due to differences in repair capabilities (Alper, 1972). Assuming that satisfactory depth dose characteristics can be achieved with neutron beams, it then follows that fast neutrons may be extremely useful in the treatment of cancer.

Optimization of neutron therapy will clearly be dependent upon the relative rates of repair of sublethal damage and repopulation of normal and malignant tissues during multifraction regimens. Experimental systems in which *individual* cells of a tissue can be monitored for viability, repair and repopulation capacity as a function of time after radiation are not yet available. However, the *in vitro* "spheroid" system (Sutherland and Durand, 1976; Sutherland *et al.*, 1971) provides a relevant model for quantitative study of these phenomena. Small multicell spheroids, in which all cells are growing rapidly, simulate normal proliferative tissues (Durand and Sutherland, 1972; Sutherland and Durand, 1976); in larger spheroids, limitations in the diffusion of nutrients lead to conditions closely paralleling those of nodular tumours (Durand and Sutherland, 1973; Sutherland and Durand, 1973; Sutherland *et al.*, 1971).

Previous work with low-LET radiation established that cells grown as multicell spheroids show a somewhat unexpected radiation response: small spheroids, in which cells differ from those of ordinary monolayers only by extensive intercellular contact, can accumulate additional damage inflicted by low-LET radiation (Durand and Sutherland, 1972; Sutherland and Durand, 1976; and Fig. 3A). As the spheroids enlarge, central cells gradually become depleted of oxygen and thus respond with typical hypoxic-cell radioresistance (Sutherland and Durand, 1973; Sutherland and Durand, 1976). Similar data characterizing the response of neutron-irradiated small and large spheroids would be of potential value both to clinicians and experimentalists; the Medical Research Council of the United Kingdom kindly offered the facilities of the MRC Cyclotron Unit at Hammersmith Hospital for the appropriate experimental work.

MATERIALS AND METHODS

Chinese hamster V79-171 cells were used in these studies. Detailed reports of growth and assay techniques for single cells and spheroids have previously been published (Durand, 1975; Sutherland and Durand, 1973; Sutherland and Durand, 1976), and were unchanged with the exception that Eagles' minimal essential medium (MEM) was used for all cell growth.

Water-jacketed spinner flasks were irradiated with fast neutrons at 120 cm from the beryllium target which was bombarded with 16 MeV deuterons. The

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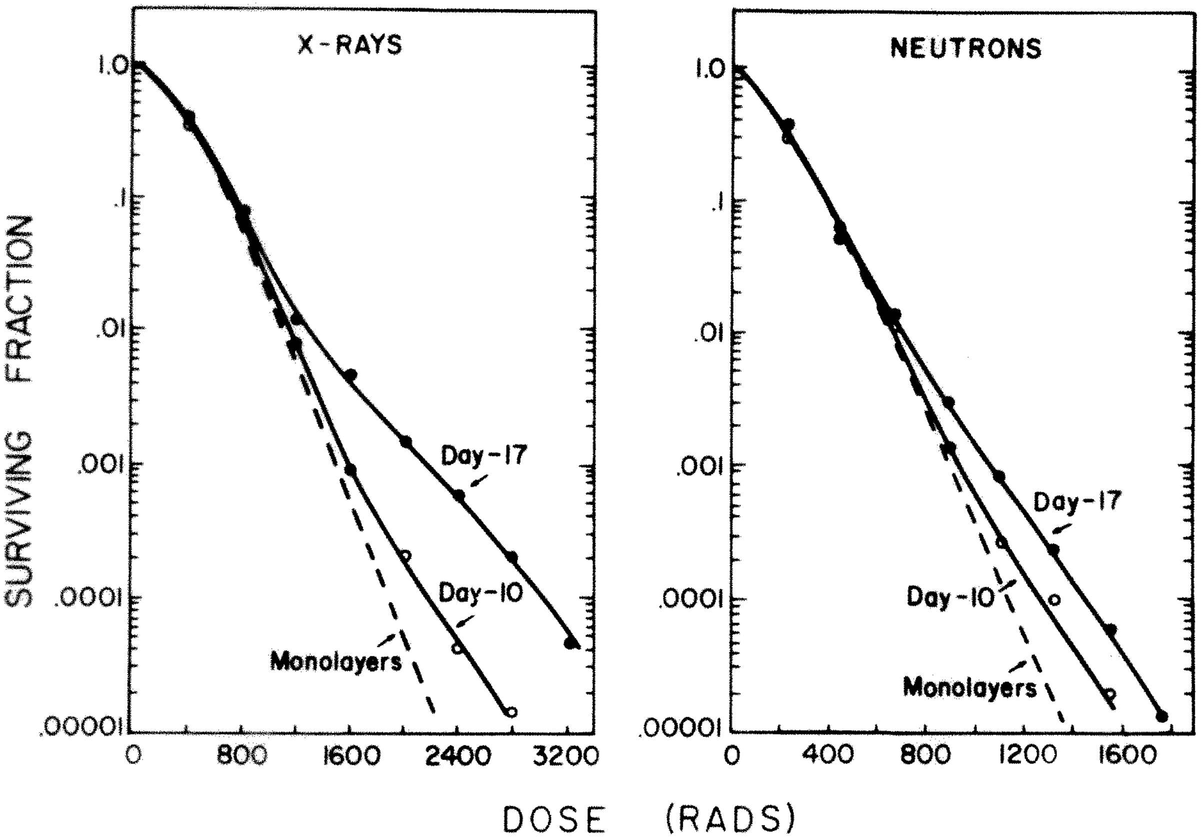

FIG. 1.

Survival of cells from monolayers (- - - -), ten-day-old spheroids (——○——), or 17-day-old spheroids (——●——) after 250 kV X-(left panel) or neutron-(right panel) irradiation. Note that the increased proportion of hypoxic cells in the older spheroids is effectively countered by the increased RBE of the neutrons.

mean neutron energy was 7.5 MeV and the dose-rate about 40 rad/min. The arrangement and geometry are discussed by Bewley and Parnell (1969). Neutron doses refer to the neutrons alone as estimated by activation of stirred $InCl_3$ solution within the spinner flasks, and are in accordance with the latest revision of dosimetry (Parnell and Bewley, 1976). In addition, there is a partial dose of γ-rays amounting to about 5% of the neutron dose.

For X-irradiation, similar spinner flasks were used. They were irradiated at 23 or 31.5 cm from the target of an X-ray tube operated at 250 kV with up to 0.3 mm Cu filter, hvl 0.5–1.3 mm Cu. The mean dose to the cells was estimated with a Fricke dosimeter, again using the standard spinner flasks. The dose rate was 240–275 rad/min.

RESULTS

Hypoxic cells of large spheroids were killed more efficiently by neutrons than by photons (Fig. 1), as enhanced cell killing was noted on the resistant portion of the multi-component survival curve. Terminal slopes of 318 and 160 rad were found for the 17-day-old spheroids irradiated with X rays and neutrons respectively. Thus, an RBE (ratio of D_0 values) of about 2.0 was observed for these hypoxic cells. Although an RBE (slope ratio) of about 1.5 was observed for oxygenated asynchronous cells (broken lines in Fig. 1, and Fig. 3, left), the gain factor for the neutron beam cannot be found by direct comparison of these numbers due to the redistribution of cells in the growth cycle which had occurred for hypoxic cells in spheroids (see Discussion, and Durand and Sutherland, 1973; Sutherland and Durand, 1976).

Repopulation in the irradiated Day 17 spheroids was followed as a function of time after neutron doses of 660 or 1100 rad (Fig. 2). The total number of cells and the number of viable cells per spheroid were both assayed at the indicated times and compared with results obtained for spheroids of the same size irradiated with ^{60}Co γ rays to similar survival levels. Regression of neutron-irradiated spheroids may have been somewhat less rapid, but only slight

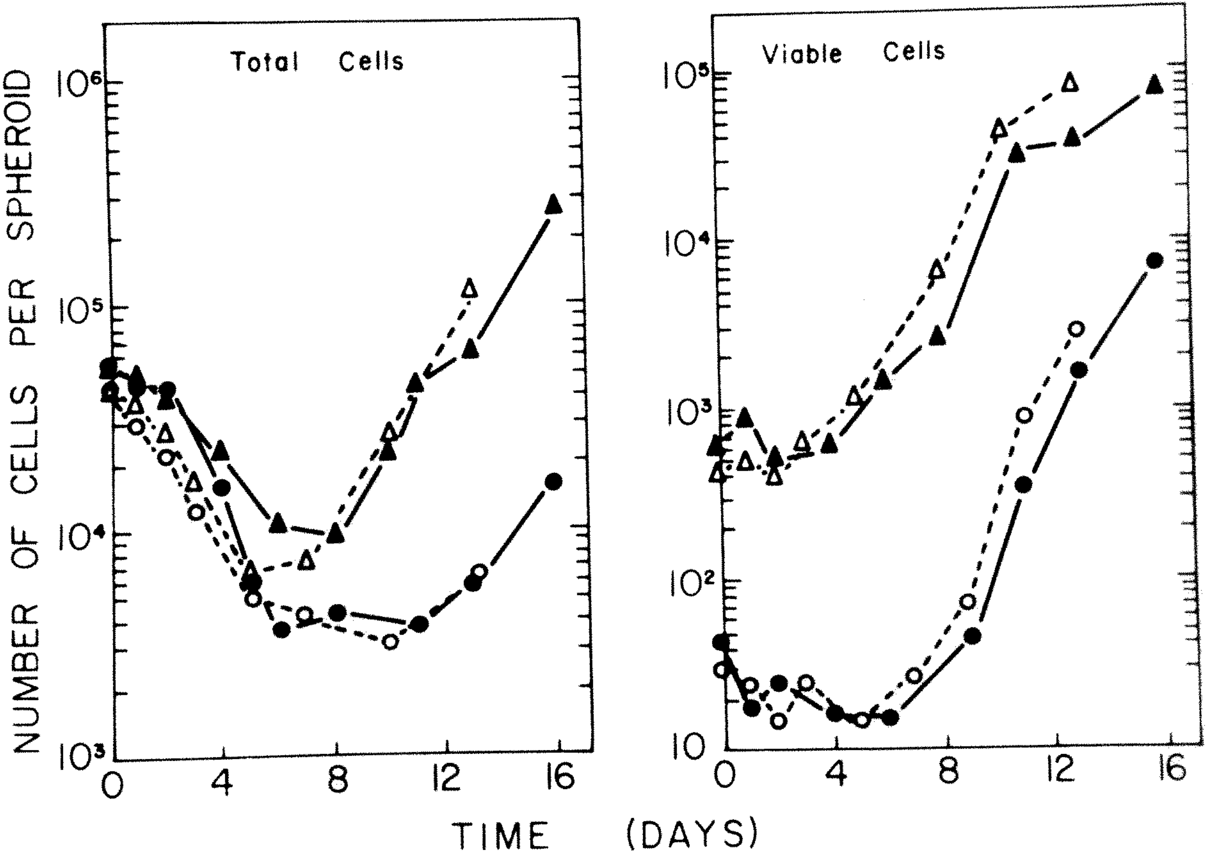

FIG. 2.

Total number of cells (left panel) or number of viable cells (right panel) per spheroid as a function of time after 660 rad neutrons (——▲——) and 1100 rad neutrons (——●——), compared with 1200 rad ^{60}Co γ rays (– – △ – –) and 2400 rad γ rays (– – ○ – –). Due to limitations of time and facilities, the panels compare two populations of spheroids irradiated at different times. The low-LET response is, however, quite reproducible, and has been matched with respect to spheroid size and surviving fraction.

differences in the initial decrease or later regrowth of the total number of cells per spheroid were observed. Regrowth of *viable* cells apparently was delayed by about one day after neutron irradiation (Fig. 2, right panel). Additional experiments with X- and neutron irradiation of the same spheroid population are, however, required to characterize definitively the kinetics of regrowth.

Survival curves for mammalian cells irradiated with fast neutrons generally have a reduced shoulder (Broerse and Barendsen, 1973; Elkind, 1970; Field, 1976; Hall *et al.*, 1975). It was thus of considerable interest to determine whether the large shoulder seen with V79 cells grown as small spheroids was still present after neutron irradiation. Compared to monolayers, an increased shoulder was observed for one-day-old spheroids (Fig. 3), although the enhanced survival seen was proportionally less than that observed with low LET-radiation. The X ray survival curves were characterized by extrapolation numbers of 9.4 and 63 for single cells and Day 1 spheroids respectively, with a D_0 of about 176 rad (Table I). After neutron irradiation, single cells were found to have $n=3.8$, whereas spheroids had $n=14.9$; the D_0 in both cases was about 115 rad.

The wider shoulder on the survival curve of the Day 1 spheroids has been correlated with an increased capability for repair of sublethal radiation damage (Fig. 4, and Durand and Sutherland, 1973; Durand and Sutherland, 1972; Sutherland and Durand, 1976). However, when two fractions of neutrons were separated by one to six hours with incubation at 37°C (data not shown) or at 22°C, no repair was observed for either single cells or Day 1 spheroids (Fig. 4). The lack of repair was independent of the neutron dose (*i.e.* at 10, 1 or 0.1% surviving fraction). One series was re-exposed after 24 hours; an increase in surviving fraction was noted, as well as an increase (~160%) in the total number of attached cells. Thus, it was impossible to conclude whether sublethal damage was repaired late during the 24-hour interval, or whether selection of viable cells or other repair processes had occurred.

Discussion

A decreased oxygen enhancement ratio (OER) can be inferred for neutron-irradiated spheroids, in agreement with results obtained for cells rendered acutely hypoxic *in vitro* and *in vivo* (Field, 1976; Field *et al.*, 1968; Hall, 1973; Withers, 1973). Unfortunately, the redistribution of cell cycle in the spheroid (prior to development of hypoxia) leads to differences in cell survival and precludes a direct measurement of the OER for the chronically hypoxic cells (Durand and Sutherland, 1973; Sutherland and Durand, 1976). Consequently, a direct evaluation of the "gain factor" (RBE hypoxic/RBE oxic) for the Hammersmith beam from spheroid data is impossible. Assuming, however, that the aerobic RBE for these cells, due to their greater radiosensitivity and reduced survival curve shoulder (Durand and Sutherland, 1973; Sutherland and Durand, 1976), is lower than the value of 1.5 observed for asynchronous cells, then the gain would be greater than 2.0/1.5, and thus unlikely to be different from the generally-observed values of 1.6–1.8 (Field, 1976) for the Hammersmith beam.

The limited data available perhaps suggest a small delay in regrowth of the cells in the tumour-like situation after neutron irradiation, even though, once initiated, repopulation appears to proceed at the same rate after X or neutron irradiation (*i.e.* slopes of regrowth curves are identical—Fig. 2). Regrowth of irradiated tumours in animal systems seems to be independent of the radiation type (see review by Field, 1976), with the possible exception of lymphoma (Berry, 1967) which regrew less rapidly after neutrons. Demonstration of a significant difference in regrowth or repopulation kinetics of tumours (or hypoxic cells?) after neutron irradiation could be

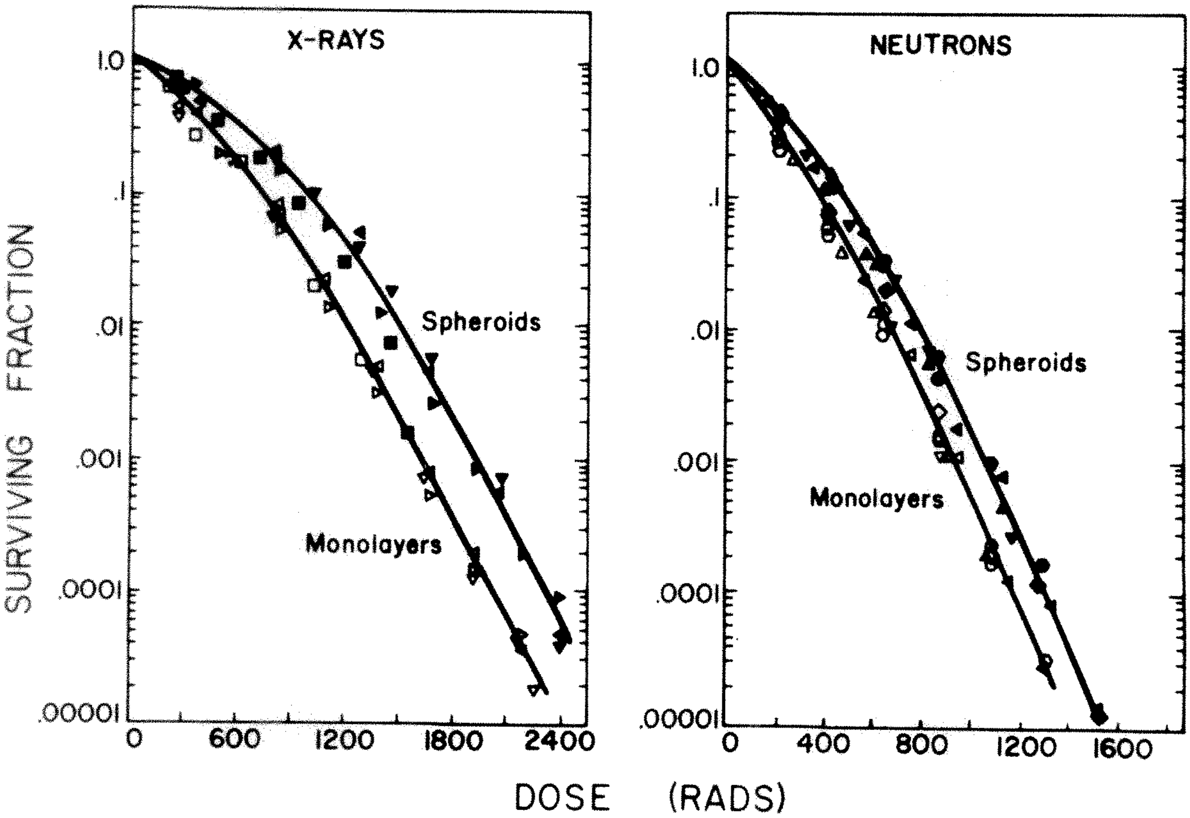

Fig. 3.

Survival of cells grown one day as monolayers (open symbols) or spheroids (closed symbols) and exposed to 250 kV X rays (left panel) or neutrons (right panel). Each symbol represents a different experiment. The parameters of the curves are shown in Table I.

important to the radiotherapist, since the repopulation rate of normal tissues seems to be more clearly independent of radiation type for a given level of damage (Broerse and Barendsen, 1973; Field, 1976).

As with X- or γ-irradiation(Durand and Sutherland, 1973; Durand and Sutherland, 1972; Sutherland and Durand, 1976), Day 1 spheroids exhibited a greater capacity to accumulate sublethal neutron damage than did single cells, as evidenced by the wider shoulder of the survival curve. It was interesting to note that the increased extrapolation number in spheroids relative to single cells for X rays (63 vs 9, Table I) was not maintained in the same ratio after neutron irradiation. Rather, the observed ratio (15 vs 4) was decreased by the same factor as was the monolayer extrapolation number for X rays vs neutrons (9 to 4), thus suggesting that the larger shoulder of the neutron-irradiated spheroids indeed reflected additional accumulation of sublethal damage. However, this enhanced ability to accumulate "sublethal" neutron damage was *not* correlated with the ability to repair sublethal damage, as neither single cells nor spheroids exhibited split-dose repair up to six hours after the initial irradiation (Fig. 4). Repair has been observed by others to proceed to various degrees, from total repair (Broerse and Barendsen, 1969; Elkind, 1970; Field, 1976; Hornsey and Silini, 1962) to no observable repair (Bewley *et al.*, 1967; Elkind, 1970; Hall *et al.*, 1975; Field, 1976; Hornsey *et al.*, 1965). Time may be an important factor in the repair processes, as pig skin (Bewley *et al.*, 1967) and mouse skin (Field, 1976) clearly begin to repair sublethal neutron damage only at long times (about 8 h) after irradiation. The additional ability of the spheroids to accumulate sublethal damage and the absence of early split-dose repair of this damage, may indicate that different types of damage and proportions of each may result from high- and low-LET radiations (Durand and Olive, 1976).

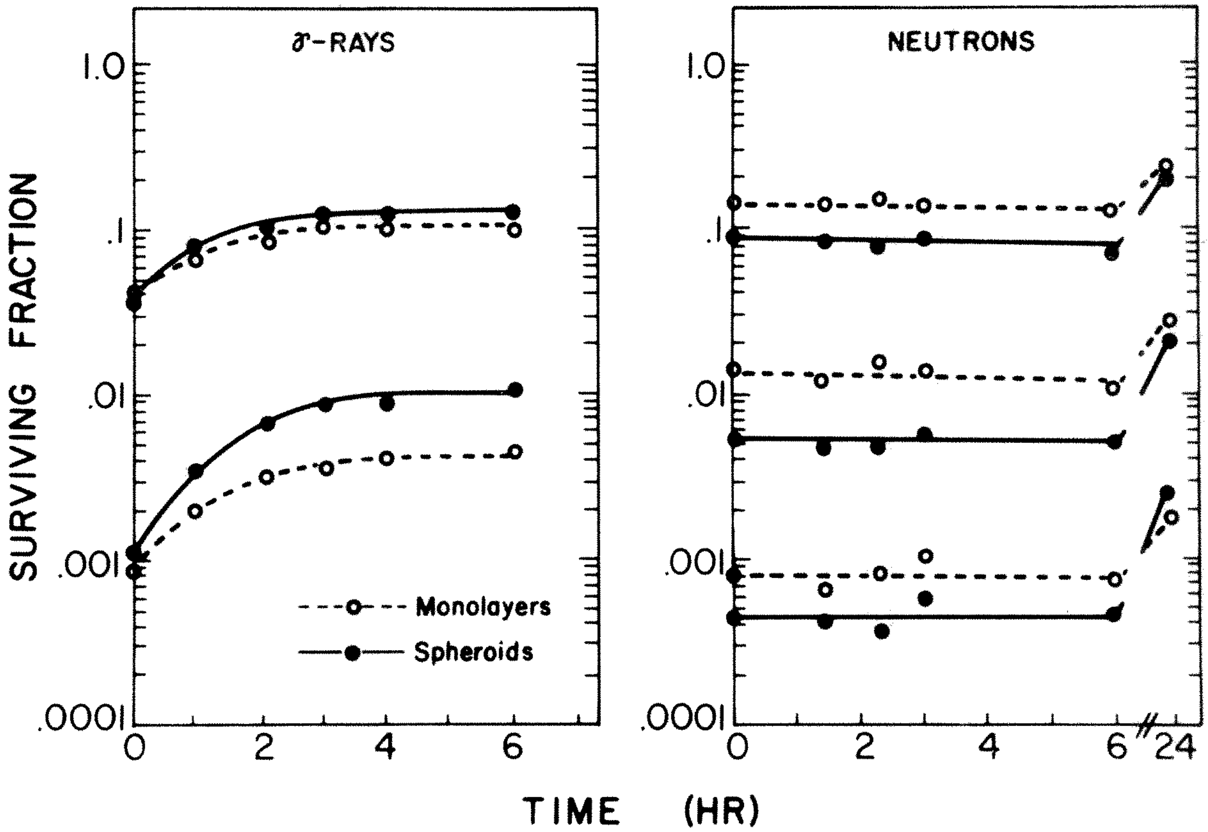

Fig. 4.

Survival of cells grown one day as monolayers (– – ○ – –) or spheroids (——●——) and then exposed to two doses of ^{60}Co γ rays (left panel) or neutrons (right panel) separated by the indicated times. The γ-doses were 2 × 450 and 2 × 750 rad for single cells, and 2 × 600 and 2 × 950 rad for spheroids. The neutron doses, designed to give 10%, 1% and 0.1% survival, were 2 × 141, 2 × 280 and 2 × 421 rad for the single cells, and 2 × 235, 2 × 374 and 2 × 521 rad for the Day 1 spheroids.

TABLE I

Parameters of X-ray and neutron survival curves

	X ray		Neutron	
	$S=1-(1-e^{-D/D_0})^{n}$*			
	n	D_0	n	D_0
Single cells	9.4	176	3.8	113
Spheroids	63	177	14.9	116
	$S=e^{-D-\gamma D^2}$†			
	a	β	a	β
Single cells	-2.67×10^{-3}	-0.99×10^{-6}	-5.4×10^{-3}	-2.19×10^{-6}
Spheroids	-1.49×10^{-3}	-1.06×10^{-6}	-4.69×10^{-3}	-1.71×10^{-6}

*Parameters obtained from survival data on linear region of curve, *i.e.* $S<0.01$ for single cells, and $S<0.001$ for spheroids.
†Parameters obtained from survival data on non-linear region of curve, *i.e.* $S>0.001$ for single cells, and $S>0.0001$ for spheroids.

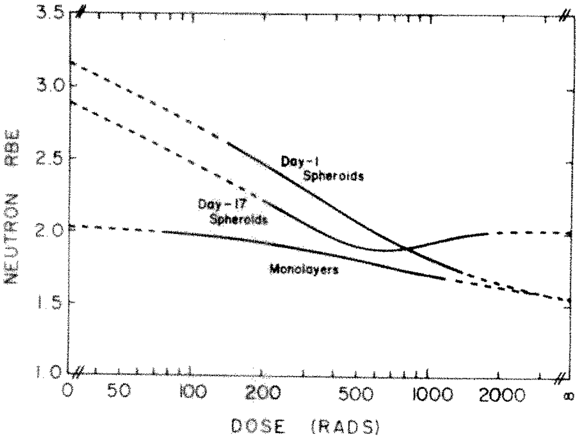

Fig. 5.

Neutron RBE as a function of dose, calculated from the best-fit curves through the data of Figs. 1 and 3. The solid lines indicate actual observations, whereas extrapolation to the limiting values (dashed lines) represent the ratios of D_0 at infinite dose, and the ratios of a (for the best-fit of low-dose data to the equation $S=e^{-D-\gamma D^2}$, see Table I) at zero dose.

The relative biological effectiveness of the neutrons (Fig. 5) was determined for single cells, Day 1 spheroids, and Day 17 spheroids from the survival curves of Figs. 1 and 3. Interestingly, the RBE curve for the Day 1 spheroids is more similar to that found for skin and gut (Broerse and Barendsen, 1973; Field, 1976) than is the single-cell curve, and thus provides additional support for the suggestion that small spheroids provide a reasonable *in vitro* simulation of some normal proliferating tissues. Note that the RBE for both the aerobic Day 1 spheroids and aerobic single cells extrapolated to a similar value of 1.5 (ratio of D_0 values) for large doses, whereas the RBE increased to 2.0 for the hypoxic cells of the larger spheroids. The extrapolations to lower doses were based on the α–β model of cellular inactivation ($S=e^{-\alpha D-\beta D^2}$), and the zero-dose value is the ratio of a for the two qualities of radiation (Table I).

If one accepts the premise that small spheroids can simulate normal tissues, and larger ones neoplastic tissues, it is interesting to observe (Fig. 5) that apparently a higher low-dose RBE for "normal" tissue than for "malignant" tissue might be predicted. The data shown in Fig. 5 are, however, observed values for single exposures; radiotherapy is generally a multifraction situation. Although no repair was demonstrated in these studies up to six hours after exposure, the suggestion of repair at 24 hours implies that the total RBE in a therapy-like situation would be a function of initial damage, repair, and repopulation kinetics. Since Broerse, Field and others (Broerse and Barendsen, 1973; Field, 1976; Field *et al.*, 1968; Fowler *et al.*, 1972) have shown that the RBE for tumours is generally greater than that for oxygenated normal tissues (in contrast to the single dose data presented in Fig. 5), it is reasonable to assume that any therapeutic advantages of fast neutron irradiation of human tumours may be at least as strongly related to repair and repopulation as to increased killing of hypoxic cells.

Acknowledgments

We wish to express our gratitude to the MRC for sponsoring this research, and to the personnel of the MRC Cyclotron Unit for their expertise and assistance. In particular, we thank Dr. S. B. Field for his efforts in making this research possible, and Beulah Cullen and Luisa Manjil for sharing their laboratory facilities. Neutron dosimetry was performed by Dr. John Parnell, and X-ray dosimetry by Mrs. Ann Sylvester. Many helpful suggestions regarding the content of this manuscript were offered by Drs. Stanley Field and David Bewley.

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When and how should we teach the basic concepts of radiation beam dosage?

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Abstract

The difficulty that many trainees, including those medically qualified, have in achieving a sound working grasp of certain basic principles of radiation beam dosage is often underestimated. Since any failure of understanding may seriously impair the efficiency of the team treating the patient, the discussion of these problems (and especially the monitoring of the results of such discussion by means of oral and written tests) deserves a high priority. Contrary to traditional practice, there would seem to be no good reason why teaching of radiation beam dosage, and the effect on dose-rate of changes in the treatment distance or in the amount of scattered radiation, should not begin in the very first week of training and be immediately integrated with discussion of the dose-rate information available at every radiotherapy unit when the patient is treated. A preliminary course of physics lectures does not usually make the understanding of these principles any easier and can be done either concurrently or later. For many radiotherapy trainees and for many doctors in other fields, comparison with drug dosage and with the brightness and scatter of ordinary light beams, avoiding technical terms so far as possible, may achieve a better initial understanding of basic principles than is achieved by mathematical equations and theoretical physics.

"*. . . common sense, not complicated mathematical reasoning. Equations occasionally crept into his argument, but in most cases words would have sufficed . . .*"

James Watson, *The Double Helix*
(Weidenfeld and Nicholson, 1968)

The basic principles of radiation beam dosage (including the effect of changes in the size of the area or volume exposed to radiation, or in the distance from the source of radiation) are essentially straightforward and non-technical, and can be grasped without any knowledge whatever of "physics" in the sense in which the word is usually used. Nevertheless, many trainees (both junior medical staff and radiography students)—and certainly doctors in other specialities—find the subject difficult and confusing.

Anyone who doubts this, or who thinks that this article exaggerates the problem, should try asking questions such as these:

1. Discuss the effect on the dose if 90% of a beam of radiation is blocked off, allowing only one small corner of it to reach the patient.
2. A patient is given 3000 rad to his left neck and 3000 rad to his right groin. Has he had a total dose of 6000 rad? If not, explain why not.
3. Which takes longer? Treating a very small area, or giving the same dose to a much larger area? Why? Explain the situation when the source-to-skin distance is the same in both cases; and also when the distance has to be increased to threetimes what it is for the small area, in order to have a wide enough beam to cover the large area.
4. Discuss and explain what sort of difference, if any, it will make to dosage received at a depth, compared with the maximum dose, if the width of a single beam (*i.e.* field size) and the treatment distance are both increased, as in the previous question.

Too often, questions such as these on vital basic principles of radiotherapy are answered badly, or not at all, by those who have been involved for many months in the treatment of patients, who have attended many lectures, who have read text books aiming to explain such things, and who have been taught all kinds of complicated theoretical physics. Medically qualified trainees start with the advantage of a much longer grounding in logical thinking and scientific method, yet may have as much initial difficulty as radiography students or technicians. Is this just a measure of a problem of comprehension, experienced by many students and doctors, but not sufficiently acknowledged? Or is it also an indication that our methods of teaching such things (and our priorities as to how much time we spend on them) are at fault?

It is sometimes said that those "who do really know" are confused by the way a question is worded, that they suffer mental blocks, or that they have difficulty in expressing what they know. These are real problems. But does anyone who has really grasped the broad principles involved, sufficiently to put them into immediate practical use whenever the need arises, have any difficulty answering questions like these? A few sentences of plain English, perhaps with a simple diagram to show the effect of changes in distance or scatter, are usually enough. Mathematical definitions, theoretical physics and specialized jargon are seldom required and may merely raise doubt as to whether the problem is understood.

A non-technical "common sense" approach to these problems, which seems to help at least some trainees, is outlined in the following paragraphs. No great originality is claimed. To underline the point that an understanding of these principles does not require any special knowledge of physics, and to approach the subject in a way intended to be as intelligible as possible to workers in other fields and to the most junior radiotherapy trainee, technical terms have been kept to a bare minimum. The object of this kind of teaching is to try and achieve a comprehension of basic concepts that is often so sadly lacking. Technical modifications and refinements, though possibly very essential to complete accuracy, are of much less importance and can be taught later. It may be objected that some of the statements made are "not strictly true", but this is hardly a valid criticism as it implies that, broadly, they are true; and it is with the understanding of broad truths that this article is concerned. Bertrand Russell pointed out that "to be perfectly intelligible one must be inaccurate, and to be perfectly accurate one must be unintelligible". It can never be a part of good teaching to use the technical jargon of exactitude when explaining vital basic principles.

Dose

Radiation trainees and workers in other specialities may well assume, until told otherwise, that a dose of radiation represents the total amount of radiation directed at the patient during the time the treatment unit is switched on. It may surprise them to learn that such a "dose" is normally neither calculated nor recorded, although it could easily be if we wished. It is as if no record was kept of the amount of a drug administered to a patient. What is the explanation for this surprising fact? The answer is that radiation dosage is a totally different concept to drug dosage. Drug dosage represents the amount administered. Radiation dosage expresses a concentration achieved. If, in a chest infection, we were to express the dose of antibiotic given in the way we express a dose of radiotherapy, we would record the average amount of antibiotic absorbed by each gram of infected lung. This "concentration" concept of dose would probably have been adopted long ago in drug therapy, as well as radiotherapy, if the necessary information was available. Whether we are talking of drugs or radiation, it is clearly more biologically relevant to know the final concentration than it is to know the amount administered. However, drugs (unlike beams of radiation) are highly susceptible to the effects of absorption, excretion and inactivation; to the movement of body fluids; and to the permeability of membranes. We can usually do little more than guess at the ultimate concentration achieved.

If the amount of radiation reaching the patient is drastically reduced by blocking off say 90% of the beam, the dose given (apart from an adjustment for scattered radiation, as discussed later) remains unaltered. This statement is incomprehensible to the person who assumes that a dose of radiation is like a dose of penicillin. But it makes sense to anyone who understands that a dose of radiation refers only to the intensity or concentration of radiation per gram in the irradiated area. If we wish to estimate the total amount of radiation absorbed by the patient, we can multiply the average dose in rad by the number of grams exposed ("integral dose"). But this exercise forms no part of normal clinical practice.

This concept of radiation dose as a measure of concentration is the first and most vital point that has to be thoroughly grasped by all radiotherapy trainees or by the physician or surgeon who would like to understand the basic elements of radiation dosage. Without it, the way in which changes in "distance" and "scatter" alter the dose cannot be understood.

For many trainees it seems that what helps most to get the message across, so that a question, like question 2 above, can be answered without hesitation, is not more mathematical equations or more theoretical physics, but plenty of discussion centred around simple analogies with everyday life. If light rain falls, not just in Glasgow but in London and Manchester as well, it may add up to a very large amount of rain, far more than if it rains only in Glasgow. But it is still light rain, it cannot be added up and called heavy rain. Moreover, to the man whose raincoat keeps him dry in light rain but not in heavy rain, it is the concentration, not the total number of gallons of rain that have fallen, that counts.

Suppose there are two neighbours, Mr. A and Mr. B. Mr. A puts three kilograms of fertilizer on his lawn, Mr. B uses less, only two kilograms on his. But if Mr. B has a much smaller lawn than Mr. A, he may have given his lawn a *smaller* amount, but a *higher* dose. For the student who finds the subject difficult, such analogies can be multiplied indefinitely. There may be twice as much sugar in two slightly sweet cups of coffee as there is in one, but the coffee is no sweeter. And so on. However, probably the most useful analogy of all is to equate radiation beam dose with the brightness of a beam of light. Block off half the width of a beam of light. The total amount of light is now only half what it was before, but the brightness (representing the "dose", or concentration, of light) stays the same. Since every radiotherapy dose represents a concentration, not a total amount, the same principle holds true when a narrow beam of radiation is used to treat, say, a small skin tumour, compared with a wide beam to treat, say, the whole abdomen. Here it has to be emphasized to trainees that, contrary to what is often assumed outside radiotherapy departments, there is no "focusing" of the beam. As much as is necessary is blocked off and wasted, leaving a narrower beam of any desired size.

To sum up: The concentration of fertilizer, the sweetness of coffee, the brightness of light (and many other analogies not mentioned, for example traffic congestion on roads or the intensity of a bombardment) are all analogous to the dose in rad or roentgens. This is because radiation beam dosage is a measure of how concentrated (or how "dilute") the radiation is when it has reached its target, a totally different concept of dose to that used in drug therapy. The explanation for this difference lies, not in any mysterious or complex properties of ionizing radiation, but simply in the fact that, in the case of a beam of radiation, such a concentration (which is clearly more relevant) can be accurately calculated and is therefore preferred. The total amount of radiation that emerges from a radiotherapy unit when a patient is having treatment depends on the time elapsing from when it is switched on to when it is switched off. But this tells us virtually nothing about the dose given. A patient who is in the treatment room for only two minutes may receive a larger dose than another patient exposed to the same radiation for much longer, say 15 minutes, even though the amount of radiation emerging per minute from the unit is precisely the same in both cases. There may be various reasons for this, but the most likely one is that a different treatment distance is being employed and this will now be discussed.

Distance

Like a beam of light from a pocket torch or flashlight, a radiotherapy beam gets progressively wider after leaving its source. At any given distance from the source, the total amount of light or radiation is the same as it was when it was nearer the source, but because it is now spread over a larger area the light is less bright and the radiation is less concentrated, in other words the dose falls. Is there any good reason why, when teaching such things, we should not describe this as the radiation being progressively *diluted* as the beam gets wider? The word "concentrated" is commonly used to refer to concentration or density in space, as well as in fluid. Why should we not use the word "diluted" in the same way? Anything that drives home the central concept of dose as a measure of concentration is worth considering, if it will make things clearer to the uninitiated.

Next it needs to be emphasized to the trainee that the Inverse Square Law, which governs the exact extent to which distance alters dose and which initially worries so many students and doctors, is really extremely simple, being dependent on nothing more than common sense and simple arithmetic. *Increasing* the distance will clearly *decrease* the concentration of radiation as the beam gets wider, so the word "inverse" is no problem. The fact that the dose is proportional to the *square* of the distance is equally straightforward in the sense that the average intelligent 12-year-old has done quite enough arithmetic and geometry to understand it. Shine a beam of light through a square aperture on to a flat surface. Double the distance and the length of the side of the square is doubled. Triple the distance and its length is three times what it was before. However, in the first case, the ***area*** is clearly not twice, but four times what it was before and in the second case nine times what it was before, thus reducing the brightness (or dose rate in the case of radiation) to only $\frac{1}{4}$ or $\frac{1}{9}$ respectively of what it was at the original distance.

A good deal of discussion and practice may be needed before trainees show, by their answers to simple questions, that they know when to employ the Inverse Square Law and how to use it quickly and efficiently. They need to be asked plenty of questions like these:

1. On an X-ray unit (for which "output" at the normal treatment distance is 60 rad per minute for a 10 × 10 cm field) you are asked to treat a patient at half the usual distance (the field size remaining the same) and you are told that the new output will be 134 rad per minute. How do you feel about this? Would you question it? Or would you accept it?
2. Two nurses watch radium being inserted. One stands one foot away for one minute, then leaves. The other stands six feet away for half an hour. Which has been exposed to the most radiation?
3. If the maximum field size at a source-to-skin distance of 50 cm is 20 × 20 cm, what is the minimum distance you would expect would be necessary in order to permit a 40 × 10 cm field to be employed?

The next point that often surprises and puzzles the new trainee or uninitiated observer is to hear that increasing the distance between the source of radiation and the patient greatly improves the dose at a depth compared with the dose on the surface, something that most people would imagine could be achieved only by using a more penetrating form of radiation. Again, it has to be pointed out to the trainee that the explanation is extremely simple and obvious if you think about it. Suppose the distance between the radiation source and the skin is 10 cm and there is a tumour 10 cm deep to the skin. The tumour is *twice* as far away from the source as is the skin and, because of the Inverse Square Law, no progressively widening beam, however powerful and penetrating, can do better than give to the tumour a miserable 25% of the surface dose. Now increase the distance to 100 cm and, instead of being *twice* as far away as the skin, the tumour is now only *slightly* further away and a depth dose far better than 25% is possible, perhaps even with a less penetrating form of radiation. The most junior trainee can now appreciate that the high depth dose of linear accelerators and other megavoltage units is due only partly to their greater powers of penetration. The longer treatment distance that can be used is also an important reason. Equally, the low depth dose of low voltage units is partly due to the short treatment distances used. No special knowledge of physics is required to understand this. The same point can be made about other important radiotherapy concepts, equally dependent only on the simple arithmetic and geometry of beams that become progressively wider as the distance from the source increases. For example, the relative importance of air gaps (the true distance to the skin being slightly greater than the intended one) at various distances; the effect of distance on the penumbra at the edge of the beam; how to calculate the extra distance required to increase maximum field size; and so on.

It seems to help students if it is emphasized that the normal "distance" chosen for each unit is a compromise between conflicting goals—a good dose rate and a good depth dose. One way to get this message across is to imagine various rather unlikely situations, for example where an X-ray unit normally used for skin tumours at a distance of 15 cm is all that is available to give urgent relief to a case of mediastinal compression. Increasing the distance to 60 cm dramatically improves the depth dose. But, if this is done, how long (the trainee is asked) will it take to give a dose normally taking five minutes? A distance of 30 cm looks like being a better compromise!

SCATTER

As with dose and distance, so with scatter, the behaviour of ordinary light beams can explain a lot of what the trainee needs to grasp, whereas learning about different kinds of atomic collision, photoelectric absorption, Compton scatter and the like, is of no practical help and need not be taught until later. If, in every radiotherapy department, there was a full scale model of the human body, solid but translucent, and if on their very first day trainees were shown how the whole body lit up slightly when even a very narow beam of light was shone into it (for example into the inner canthus of the eye, as in the treatment of a rodent ulcer at this site), it would provide an instant and impressive demonstration of the fact that nothing can prevent a small amount of the radiation in a beam from scattering in all directions within the body. At the same time, it could be shown (by comparing the situation with that seen when light is shone on to the surface of an *opaque* body, or through a *thin* piece of a translucent substance) how light scattered back to the surface added to the brightness of the beam at the point where it entered the body, thus demonstrating the additional surface radiation occurring in radiotherapy as a result of "backscatter".

The traditional but very misleading term "output" now has to be explained to the trainee. It would have been much less confusing if this term had been strictly reserved for the amount of radiation emerging per minute at the source. This would correspond with normal usage (for example when we speak of the output of a factory) and could be used when megavoltage output is being compared with low voltage output. But, as emphasized (some will feel unnecessarily laboured) already, output in this sense is the one thing that the dose rate in rad is not. It would be bad enough if the word was used for the dose-rate in air at varying distances from the source. Its use to describe the vital concept of incident (*i.e.* surface) dose, *including backscatter*, is even worse. My colleague, Dr. Stewart Orr, has suggested to me that a change to "input" might help to make things clearer. But for the present we seem to be stuck with "output", illogical and misleading though it is.

The dose-rate is different for different areas (trainees need to be told) because a gram of surface tissue in the centre of a wide beam is inevitably subjected to more scattered radiation (both from deeper tissues and from the beam collimator) than if it was in the centre of a narrow beam. This is the only reason. If it was not for such scatter, dose-rates would be the same for every field size and conventional "output charts" could be dispensed with.

If it was not for scatter, "output" would be as constant and unvarying for different field sizes as is the brightness of a beam of light when it is shone onto an opaque surface and varying amounts of the beam are blocked off. Once trainees have really understood this point they will not make the serious mistake of thinking that it is just the width of the beam emerging from the radiotherapy unit (as determined by fitting a particular applicator or using a particular jaw setting) which decides how "output" varies with field size. The properly trained member of staff will know that, although the effect is sometimes so small that it can be ignored in clinical work, *any* change in the size of the area exposed to radiation *must* change the dose-rate, because it changes the amount of scatter; and that this must be so, regardless of whether the "blocking off" of part of the beam occurs inside the unit, on a tray set in the path of the beam, or by means of a "cutout" resting on the patient's skin.

Finally, the extra scatter coming from all directions explains why a wider beam gives a better depth dose, as well as a better surface dose rate, and why this effect increases with increasing depth.

Discussion

There can be no argument about the importance of every member of the radiotherapy team being clear about these basic concepts. Increasingly, as we move into an age of calculators and computers, the well-trained member of the team will be the one who can be relied upon to question any dose-rate adjustment or other instruction that does not square with basic principles. Questions on these principles should surely appear in all qualifying examinations and should be compulsory, not optional.

When it comes to teaching, the first point is not to underestimate the difficulties experienced by many trainees. We need to be realistic and to consider carefully, not what we think ought to be understood by a trainee after a lecture, but what close questioning shows has in fact been understood. The only way to monitor progress is to have ready plenty of questions, framed so far as possible to test comprehension rather than memory. Memorizing and then writing down correctly the definition of the rad or the roentgen is one thing. Showing a real working grasp of the fact that each is a unit of concentration, not total amount, is quite another. Equally, trainees who can correctly write down a mathematical equation representing the Inverse Square Law may be a long way from being able to use it when some simple practical problem arises, such as doubling the treatment distance or halving it. Somehow these mental gaps have to be bridged if training is to be realistic and efficient. And we need to get our priorities right and consider if it makes sense to talk to trainees about thermionic emission, angstrom units, quantum theory, or K, L and M rings, if they have been working in radiotherapy departments for months without ever really understanding what "output charts" are all about. Is there any good reason why these things should not be taught from the very first day a trainee enters a radiotherapy department? Then discussed, demonstrated, and mulled over with the aim that every trainee will have a fair understanding of them within two or three months? To do this would underline the fact that no special knowledge of physics is required. It would also allow the trainee to appreciate from the very start of his training that what is discussed in lectures can be immediately integrated into what actually happens when a patient is treated.

To gain their full co-operation all trainees need to be told the vital importance, if they are to be safe and efficient members of the radiotherapy team, of gaining an early understanding of these basic concepts; they need to be reassured that, if they get confused, they are in good company; and warned that a good deal of repetition, discussion and questions may be necessary. Teachers and taught may become equally frustrated by the need to keep going over the same ground and both will look forward to getting on with something different. The approach suggested is only one way of teaching these things. No doubt to some teachers and to some trainees it may seem neater, clearer, and more accurate to express such concepts in a more mathematical form. It may help to have several lecturers tackling the problem in different ways. Only discussion and questioning will show the degree of success achieved at any given time.

Finally, much more could be done to explain, in non-technical language, the basic concepts of radiation beam dosage to workers in other specialities, many of whom have never been told the fundamental difference between radiation dosage and drug dosage. Such misunderstanding can result in various kinds of inaccuracy and confusion, including the adding together of doses given to different parts of the body.

Acknowledgments

It is a pleasure to thank Dr. J Stewart Orr, Chief, Physics Division, and Miss Joan Miller, Principal, School of Radiotherapy, for their comments and for helpful discussion of these problems.

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Technical note

A new method of immobilization of patients for radiotherapy

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The importance of immobilizing the patient during radiotherapy has been recognized for many years. This is particularly so when the radiation beam is horizontal, as is the case with many neutron generators at the present time, but immobilization is still important for adjustable beams when accurate alignment is needed.

One reason why immobilization is not used more often is the time and expense involved. A commonly used method involves three separate steps: the taking of an impression of the patient with plaster of Paris bandage, construction of a plaster cast, and formation of a plastic shell with a vacuum forming machine. The present note describes a one-step process based on an orthopaedic material called Lightcast (Merck, Sharp and Dohme Ltd).

FORMATION OF THE IMMOBILIZING MASK

The Lightcast material is an open-weave, flexible, fibreglass tape impregnated with a photo-sensitive resin which remains in a soft flexible state until exposed to ultraviolet light. It can be easily moulded round the patient in the soft state and is then hardened before removal by exposure to the ultraviolet light for a few minutes. It then becomes strong and rigid. The tape can be obtained in widths from 2.5 cm to 15 cm and 2 m long and is packed in sealed sachets.

The ultraviolet lamp supplied by the manufacturer generates light in the region 350–390 nm. The lamp remains cool during operation and the manufacturers claim it to be safe under the conditions of intended use (Corvi *et al.*, 1972).

The tape is applied to the patient in a similar way to plaster of Paris. The patient's hair, apart from the scalp, is covered with paraffin gauze (Jellonet) and any area of skin that will be in contact with the Lightcast is lightly covered with Dimethicone (silicone) cream. The eyes are also covered, first with a small pad of dry gauze and then with some paraffin gauze which covers both the dry gauze and the eyebrows. The reason that the eyes are covered in this way is that when Lightcast is soft it gives off vinyl toluene vapour and may cause smarting of the eyes. The hair of the scalp is usually covered in two layers of tubular bandage.

The layers of tape are usually applied from the top downwards. Layers are overlapped slightly and gently pressed together to obtain good adhesion. Generally two to three layers of tape are required for a strong rigid mask. The ends of the tape can be carried around the side of the patient's head and attached to fixing points on a headboard. These fixing points ensure that the mask is fixed firmly and reproducibly (Fig. 1).

The process of curing by the ultraviolet light takes three to five minutes at a distance of 10 cm from the lamp. Once hard, the Lightcast may be cut with tin-snips and any sharp edges filed. Sharp edges are also avoided by folding the edges before curing. The Lightcast in its uncured state conforms to body contours well, although the fine detail such as eyebrows and wrinkles which are retained with Bexoid shells are lost. The final degree of immobilization is the same with either type of mask.

THE ADVANTAGES AND DISADVANTAGES OF THE SYSTEM

This system has been in use for the past two years for the immobilization of patients treated with the fast neutron beam at the Medical Research Council's Cyclotron Unit at Hammersmith Hospital (Catterall *et al.*, 1975). Over 150 face masks and other immobilizing devices (*e.g.* body jackets, buttock supports) have been made. All retained their shape and remained rigid throughout the whole course of treatment. No patients complained of the smell of the vinyl toluene vapour.

Lightcast is difficult to mark partly because of the open weave and partly because of contamination by the silicone cream. It is also difficult to use adhesive strip to attach radiographic markers. However, plasticine has been found to be a satisfactory alternative.

The average time taken to make a face mask is half an hour and simulation of treatment can follow immediately. Radiographs of patients wearing Lightcast masks during simulation were found to show

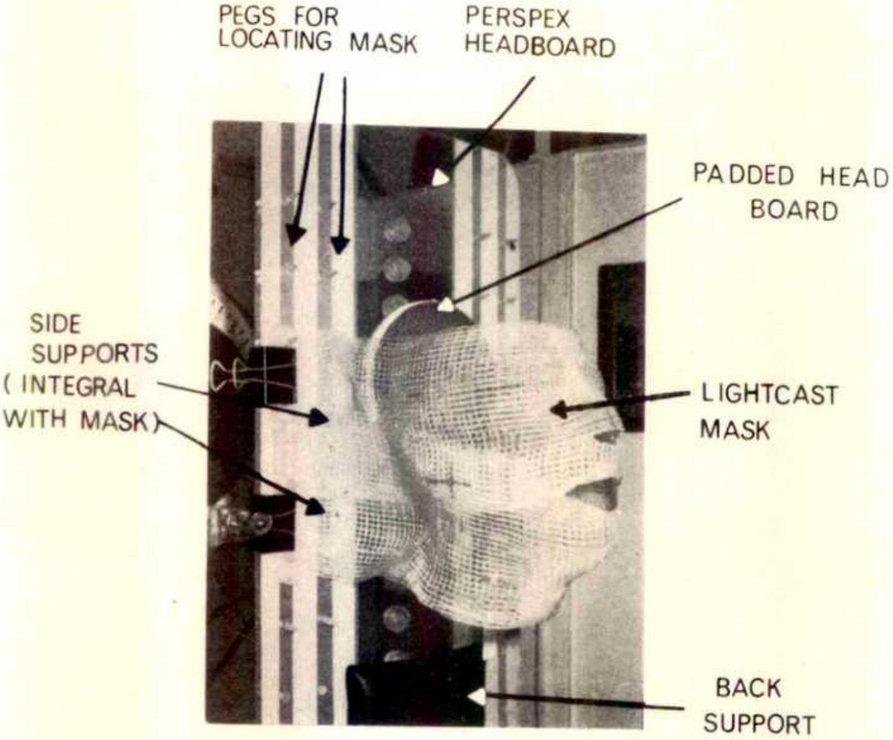

FIG. 1.
A Lightcast mask shown attached to the patient's headboard.

some gridded overlay from the weave of the fibreglass which, although clearly visible, caused no loss of anatomical detail.

Patients treated at the Hammersmith cyclotron with fast neutrons are treated with a beam that is fixed and horizontal. With such a set-up, patients with head and neck tumours are usually treated in the sitting position. Immobilization is therefore of paramount importance. Bolus material is often required and the Lightcast forms a rigid support for this. Because Lightcast is an open weave, it allows the patient's skin to breathe and they feel less claustrophobic than in a Bexoid shell.

CONCLUSIONS

1. The merits of this system are that it is rapid and only one visit by the patient is necessary. This is a great advantage to the elderly and those suffering from advanced malignant disease.
2. Masks retain their strength and shape during treatment.
3. The cost of the equipment is very much less than the vacuum forming machines required for Bexoid shells. A typical hand Lightcast lamp costs £400 and the tape costs £12 for a carton of ten rolls.
4. The system is very easy to use and therefore trained personnel are not required.

ACKNOWLEDGMENTS

I should like to thank Mr. D. K. Cooper of Merck, Sharp and Dohme Ltd, for his continued support in supplying the Lightcast lamp and tape. I am also very grateful for valuable advice and guidance from Dr. Mary Catterall, Consultant-in-charge, Fast Neutron Clinic, Hammersmith Hospital.

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Case reports

The radiology of Fournier's gangrene

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In 1884 Fournier described five patients with acute idiopathic gangrene of the scrotum characterized by rapid onset and progression. Approximately 100 cases have been reported. It occurs mainly in healthy men between the ages of 20 and 50 (Burpee and Edward, 1972), but has occurred as early as four months of age (Soong and Whee, 1966).

CASE REPORT

A 30-year-old Asian male was admitted complaining of pain, tenderness and swelling in the right groin and scrotum. Eight days previously, he had been in hospital because of a possible splenic rupture following a car accident. A right femoral artery puncture for selective splenic arteriography was performed. The examination was normal. He was asymptomatic until two days before readmission when he developed a right scrotal mass. He was also febrile with shaking chills.

On admission a small area of redness was noted over the right groin, medial to the site of the arterial puncture. The puncture site itself was not inflamed. Radiographs showed oedema with scattered irregular air densities over the right side of the scrotum (Fig. 1). The patient was diabetic and received 60 units of Lente Insulin each day.

He was placed on intravenous fluid therapy and antibiotics. His temperature fell but he continued to complain of pain and tenderness (Fig. 2).

Two days after admission his temperature again rose. Incision and drainage was performed. Culture and sensitivity studies revealed a mixed bacterial pattern including bacteroides, anaerobic streptococcus, and staphylococcus epidermoids. He was discharged on the 17th hospital day following a 48-hour afebrile period.

DISCUSSION

Scrotal infections are similar to those of skin and subcutaneous tissues in other parts of the body, but some differences occur because of the structure of the scrotal wall. The scrotal skin is traversed by deep transverse folds. There are numerous sweat glands, and the skin is moist.

Because of its location, scrotal skin is relatively inaccessible to air, and surface contact with the adjacent thighs is often a deterrent to healing. Bacteria are prevalent, but fortunately there is local tissue resistance to these organisms. The loose, fat-free and contractile scrotal wall reacts to inflammation with considerable oedema. The tense skin causes excoriation and interference with vascularity. However, healing occurs after most surgical infections.

Scrotal gangrene may be due to many causes, including instrumentation, urethrocutaneous fistulae, penile erosions, prostatitis and epididymitis. Spontaneous gangrene with pre-existing urinary tract disease is reported.

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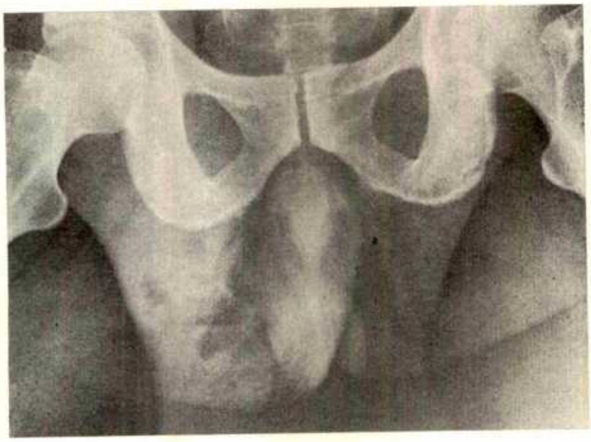

FIG. 1.

Coned-down view of the scrotum shows air density intersecting the soft tissues.

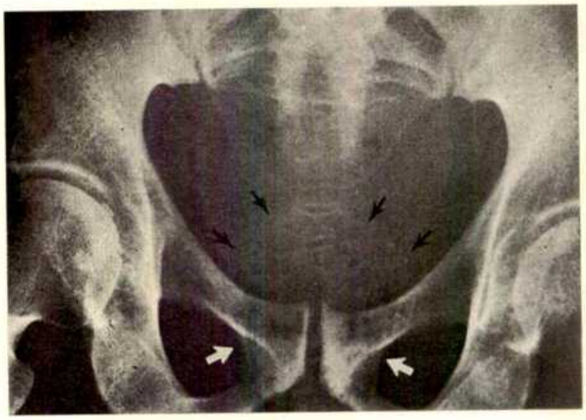

FIG. 2.

Later radiographs of the pelvis shows air about the prostate and bladder related to extension of the gangrene.

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Before the use of modern antibiotics the mortality was between 22 and 31%, usually related to toxaemia (Mansfield, 1945). Deaths are now rare. The gangrenous process is usually limited to the scrotum but may spread under Collier's and Scarpa's fascia into the abdomen (Campbell and Harrison, 1970). It rarely involves the vas deferens or testes.

The radiological findings are those of marked swelling of the scrotal tissues together with air densities in the interstices of the scrotum. These findings must be distinguished from other causes of pneumoscrotum, including gangrene of a known aetiology, injury to the urethra or scrotum after trauma, and anastomotic leakage after anterior resection of the colon (Castellano *et al.*, 1973). It must be distinguished radiographically from herniation of bowel loops into a scrotal sac.

Fournier's gangrene may be related to an underlying antecedent cause. Diabetes, alcoholism and general debility have been implicated. In our patient diabetes mellitus may have played an important part in the development of the inflammatory process.

An alternative explanation for the condition is vascular thrombosis related to infection and analogous to cavernous sinus thrombosis. The infections may be due to organisms entering the skin through minute abrasions or embolic bacteria from remote sites.

Most cases present with pneumoscrotum and gas is often encountered on surgical incision.

The bacteriology of Fournier's gangrene is incompletely understood but anaerobic streptococcus has been the most frequently found organism.

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Gas nephrogram: an unusual complication of renal transplantation

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The major complications following renal transplantation often call for selective angiography, venography and ultrasonic examination (especially of a palpable mass at the site of transplant). Functional status can be assessed by an intravenous excretion urogram or isotope renogram. We present an unusual plain film diagnosis.

Case History

A woman aged 53 years had a well-matched cadaver kidney transplanted into the left iliac fossa in July 1975, following two months of maintenance dialysis for renal failure caused by rapidly progressive glomerulonephritis. Two early rejection episodes were treated with methylprednisolone, and maintenance was with prednisone and azathioprine. She developed insulin dependent diabetes, and for five days after discharge had a mild leucopenia. She was discharged after four weeks with a serum creatinine level of 336 μmol/l.

One week later she was re-admitted with staphylococcal skin sepsis and deteriorating renal function. Following further methylprednisolne serum creatinine stabilized at 600 μmol/l.

A transplant biopsy was performed and this showed some necrosis of the renal parenchyma; in view of the residual renal function this was presumed to be patchy. The kidney at that time did not appear enlarged or tender, but after two weeks a palpable perinephric mass developed over the upper pole. Attempted aspiration brought out some gas. To exclude accidental perforation of the colon radiography of the abdomen was carried out.

Radiographic findings

The transplant kidney was very well demonstrated by inherent contrast due to collections of gas within the necrotic renal parenchyma. There was a cavity adjacent to the upper pole, which showed a gas/fluid level on the radiograph in the erect position. A diagnosis of transplant sepsis with localized abscess formation was made. An I.V.P. only showed poor excretion in her own kidneys.

At transplant nephrectomy a totally infected necrotic kidney was removed. A radiograph of the excised kidney confirmed the presence of gas in the renal parenchyma, and histological examination showed gram negative bacilli. A wound infection by pseudomonas and proteus organisms followed but slowly recovered.

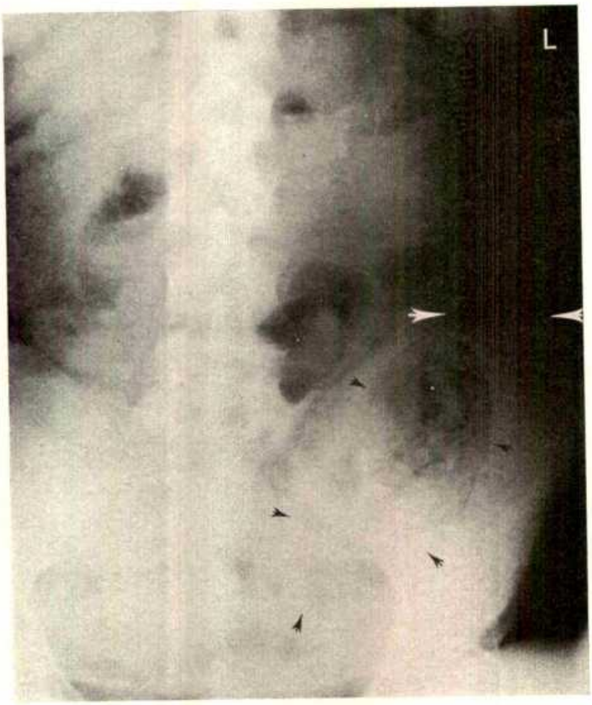

FIG. 1.

Erect radiograph of the abdomen showing the transplant kidney clearly outlined by gas in the renal parenchyma (black arrows). Gas and fluid level in the perinephric abscess (white arrows) near the upper pole of the kidney. Several fluid levels are shown in the large bowel.

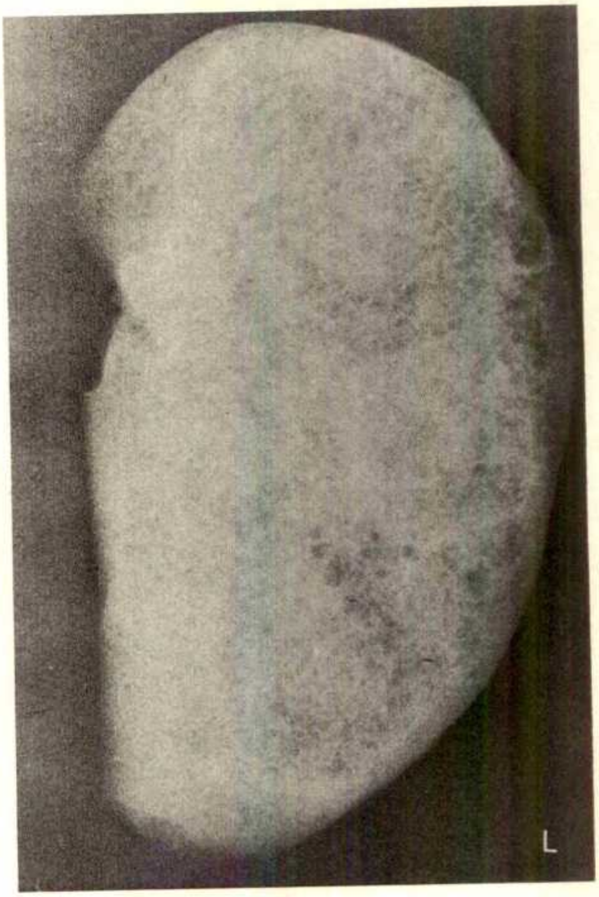

FIG. 3.

Radiograph of the excised transplant kidney showing parenchymal collections of gas.

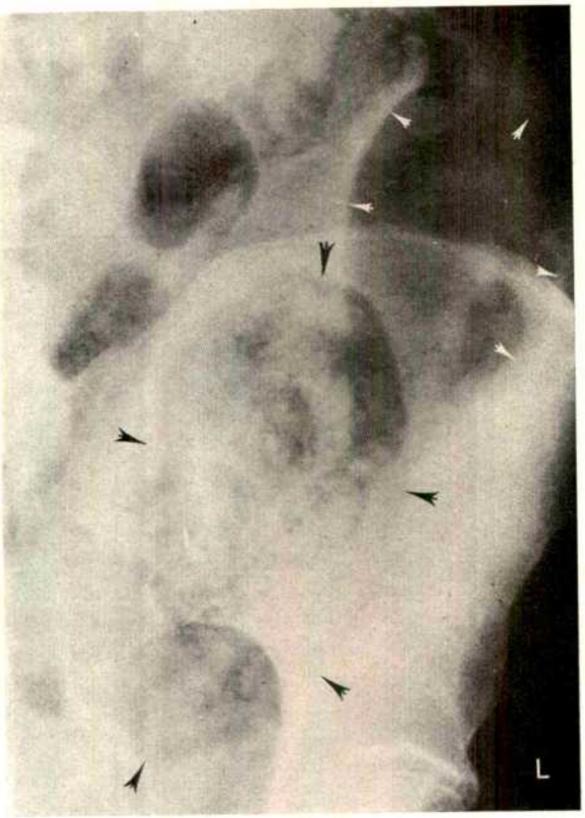

FIG. 2.

Enlarged view of the gas filled transplant kidney (black arrows) and the abscess (white arrows) in supine position.

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DISCUSSION

Sepsis in various forms is still considered as an important and common complication of renal transplantation. Several reports concerning wound infections and sepsis after renal transplantation have appeared in the medical press recently, and a detailed analysis of 27 cases with wound infection and subsequent sepsis has been reported by Kyriakides *et al.* (1975). In 24 cases of perinephric abscess after cadaver kidney transplantation the highest incidence was in diabetic patients between 3rd and 4th decades of age. Almost half of the infected wounds had developed a haematoma which required drainage following surgery. All cases with deep infection had either a leak or a perinephric haematoma. Gram negative organisms were isolated from all cases, and in 50% E. coli was the dominant organism; 55% of cases required transplant nephrectomy. In a report from Denmark (Walter *et al.*, 1975) indwelling drainage tubes were believed to be the cause of wound infection in 18 out of 53 cases.

The inherent contrast contributed by the presence of gas within the kidney and the fluid level in a cavity outside the kidney helped in the diagnosis of our case. The pattern of collection of intrarenal gas clearly outlined the entire kidney. Differentiation from a loop of colon filled with gas and faecal matter could be difficult unless the collection of gas outlines the whole of the kidney giving it the appearance shown in our case. Individual radiological demonstration of colon and kidney should settle the diagnosis in difficult cases.

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Unusual presentation of non-parasitic hepatic cyst

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Large non-parasitic hepatic cysts are rare. It is rarer still for them to show radiologically as avascular areas, surrounded by dense curvilinear shadows on urography and for the diagnosis to be made before operation. A "halo" sign shown during urography has not previously been described.

Liver cysts may have their origin from aberrant bile ducts in the liver; these ducts represent embryonal rests and have been found only in cystic livers or livers associated with cystic kidneys. They may assume two forms, one arising from inflammatory hyperplasia of their ducts and the other by retention of fluid in these ducts or as the result of congenital obstruction. They are subcapsular and are filled with watery fluid containing albumin, mucin, cholesterol, epithelium and granular debris. Bile-pigment is generally absent (Boyd, 1913). Alternatively the fluid may be thick bile, blood or pus (Henson *et al.*, 1956). Simple cysts rarely reach sufficient size to cause symptoms. The lesion may occur at any age. Most patients described in the literature have been in the fourth or fifth decades. Females are affected more frequently than males. The ratio is three or four to one (Caplan and Simon, 1966). The right lobe is involved approximately twice as often as the left (Geist, 1955). They are frequently associated with polycystic disease of the kidney and occasionally are accompanied by cysts in the pancreas and spleen (Comfort *et al.*, 1952; Deutsch, 1953).

Liver cysts rarely cause symptoms and are compatible with life. Occasionally patients with liver cysts may present with pain, pyrexia (Davis, 1936), symptoms due to pressure on the surrounding structures (Stock, 1952), associated cholecystitis (Deutsch, 1953), cholelithiasis (Henson *et al.*, 1956) or jaundice (Henson, 1963; Dardik *et al.*, 1964).

If the cysts are large enough they may displace the right kidney medially (Geist, 1955), or the left kidney may be displaced downwards by a left hepatic cyst (Henson *et al.*, 1956). Gall-bladder displacement has also been reported (Geist, 1955). At oral cholecystography displacement and pressure defects on the gall-bladder by a cystic liver have also been described by Sandy (1965) and Anton (1972) whereas at barium enema examination downward displacement of the colon by a cystic liver has been described by Geist (1955). Elevation of the diaphragm, deformity of the stomach and calcification of the cyst have been reported by Henson *et al.* (1956). A non-parasitic cyst of the liver may undergo torsion and sometimes rupture (Morgenstern, 1959). Other complications like infection and haemorrhage into the cyst may also occur.

CASE REPORT

A 63-year-old Burmese lady was admitted to the Rangoon General Hospital on 5.11.71 with severe right-sided abdominal pain. On examination she was febrile and her abdomen distended. A tender mass was palpable in the right lumbar region about the size of a grapefruit. On questioning her further, she gave a history of having noticed the lump for more than five years but of not having sought medical advice because it was not troubling her. She was not jaundiced. Laboratory investigation was not remarkable except that her E.S.R. was raised. Liver function tests were within normal limits, Kahn test normal and serological test for syphilis negative. Blood urea was 40 mg/100 ml.

Radiological investigations

Plain X-ray of the abdomen (Fig. 1). A soft tissue mass was shown in the right side of the abdomen. The psoas shadows and the renal outlines were not visualized. There were small multiple opacities in the left side of the abdomen resembling gall-stones, but this would have been an unusual situation for gall-stones. The possibility that they were calculi in a hydronephrotic kidney was therefore considered and intravenous urography carried out.

Urography

The patient was dehydrated and a rapid injection of 40 ml of Urografin 76% carried out. The five-minute radiograph showed two large avascular areas in the liver region, with relatively dense curvilinear opacities surrounding them. Compression was released and a further 60 ml of Urografin 76% injected. This enhanced the appearance seen on the five-minute radiograph and persisted for more than 40 minutes (Fig. 2). The renal outlines and pelvicalyceal systems were normal except that the right kidney was displaced across the spine to the left and anteriorly. The opacities in the left side of the abdomen were shown to lie outside the urinary tract. With these findings it was concluded that the masses, which were probably of a cystic nature, originated

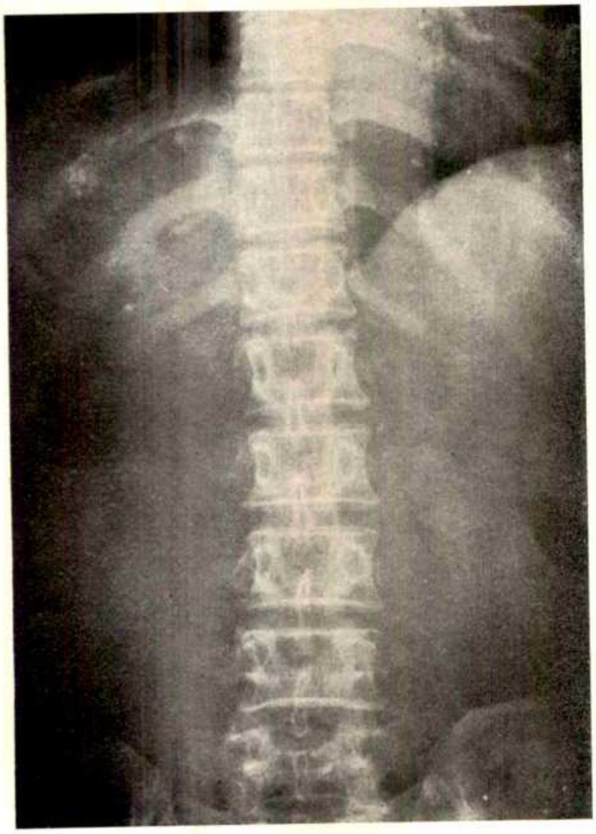

FIG. 1.

Mass in the right side of the abdomen and calcification on the left.

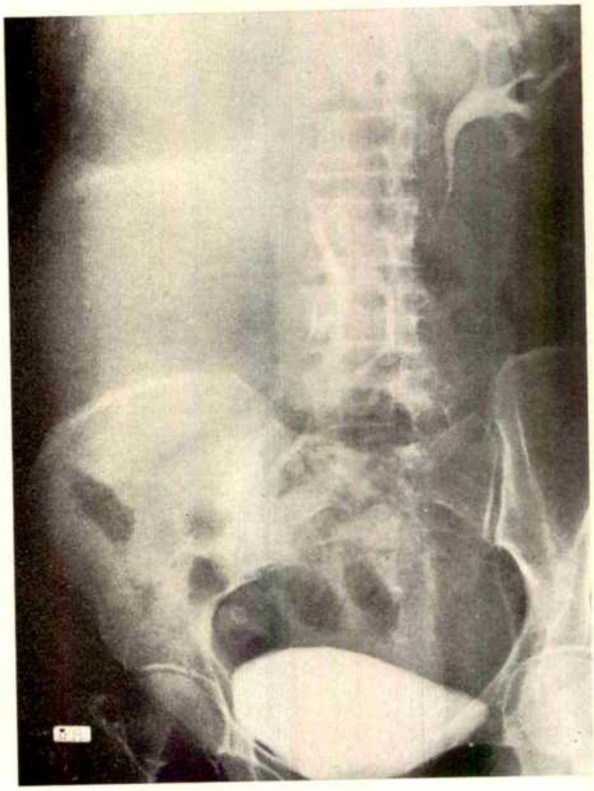

FIG. 2.

Forty-five minutes after the second injection. Oblique view showing the outline of the cysts. Lateral view showed the outline of the cysts. Anterior displacement of the right kidney and gall-stones.

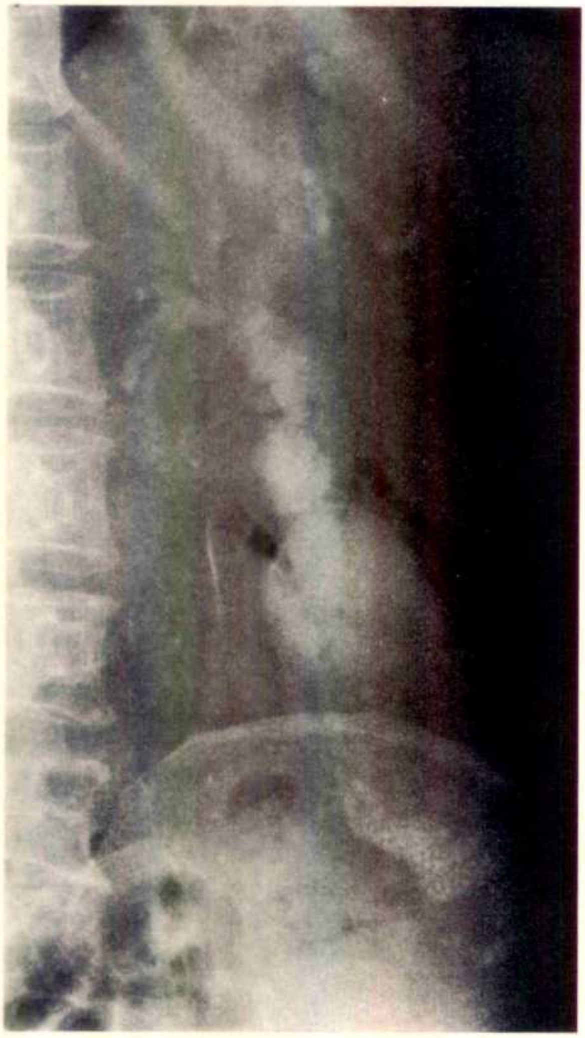

Fig. 3.

The gall-bladder is displaced into the left side of the abdomen. Dilated common bile duct and gallstones are shown.

from the liver and were displacing the right kidney and gall-bladder containing gall-stones to the left side. For confirmation an intravenous choledochogram was performed. This revealed a poorly concentrating gall-bladder with dilated cystic and hepatic ducts with cholelithiasis (Fig. 3). A liver scintigram with ^{131}I rose bengal (Fig. 4) showed large defects corresponding to the mass and cystic lesions seen on the plain radiographs of the abdomen and on urography. The chest radiograph showed an elevated right hemidiaphragm and obliteration of the right costophrenic angle due to pleural adhesions. Both lung fields contained scattered calcified foci (Fig. 5).

Treatment

At laparotomy there were two large cysts approximately 13 cm in diameter, one arising from the supero-anterior surface and the other from the antero-inferior surface of the right lobe of the liver. The latter was causing displacement of the right kidney and gall-bladder to the left. A smaller

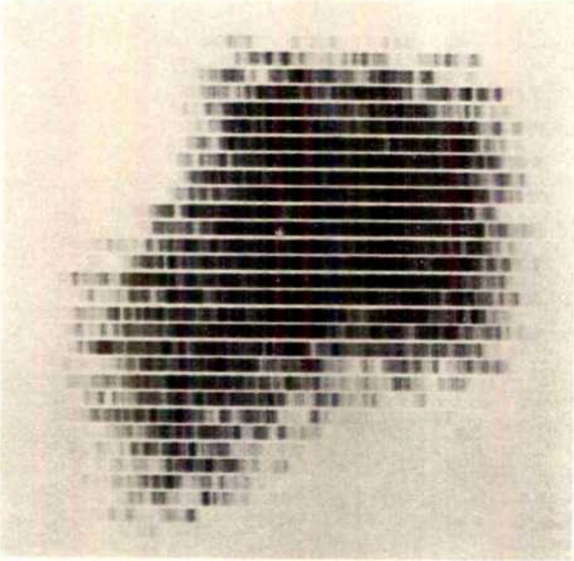

Fig. 4.

Areas of negative uptake are seen in the right lobe of the liver.

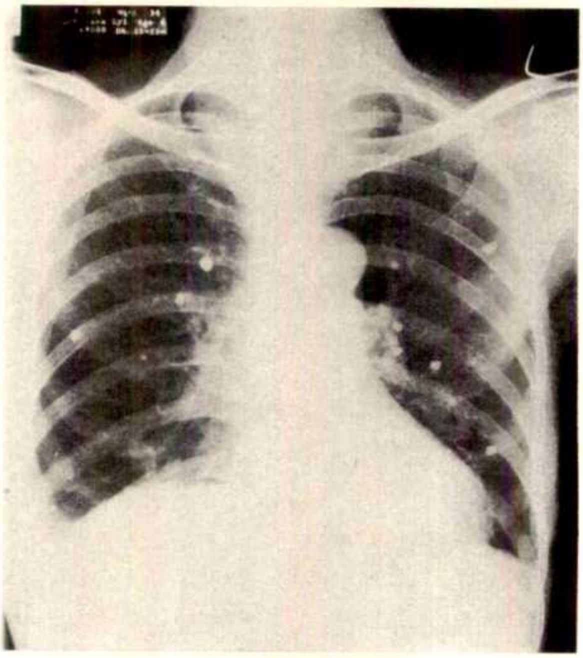

Fig. 5.

Chest, showing pleural thickening at the right costophrenic angle with elevation of the right hemidiaphragm and calcified pulmonary foci.

cyst, 3 cm in diameter, was seen between the two large cysts situated medially to them. The liver showed changes of early cirrhosis. The cysts were marsupialized and cholecystectomy was performed. The patient made an uneventful recovery.

Histology showed that the cysts were lined by low columnar epithelium resembling biliary duct cells.

DISCUSSION

A "halo" sign, *i.e.* an avascular area surrounded by a densely opaque curvilinear opacity has been described in angiography of the liver in hydatid disease (James, 1968; Baltaye and Richard, 1970; Gnassan *et al.*, 1971; McLoughlin and Gilday, 1972). This appearance on coeliac axis angiography occurs since the outer layer of the parasitic cyst is vascular enough to retain the contrast medium for some time; or it could be due to compression of liver cells by the cyst.

Total body opacification in infants has been described by Griscom and Neuhauser (1966) and could be used in suspected cases. Hepatoma and hepatic cysts have been shown at these investigations (O'Connor and Neuhauser, 1963; Martin, 1972; Holt *et al.*, 1965).

A small amount of contrast medium 0.5–2% can be excreted through the liver and gall-bladder without being conjugated with plasma protein (Cattell, 1970). It is thus possible to outline a non-parasitic hepatic cyst on intravenous urographic examination, when the histology of the cyst and the technique of injection have provided favourable conditions for the "halo" sign to appear. The size of such cysts also play an important role in giving this appearance.

SUMMARY

A case of non-parasitic cyst of the liver, lined by bile duct epithelium has been presented. The cysts were shown as avascular areas each surrounded by a dense curvilinear opacity ("halo" sign), causing displacement of the right kidney anteriorly and to the left of the spine. The gall-gladder with cholecystitis and cholelithiasis was also displaced to the left of the spine. There was elevation of the right hemidiaphragm with inflammatory changes in the base of the right lung. The scintigram revealed defects caused by the cysts.

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An unusual ultrasound appearance of a hydatidiform mole

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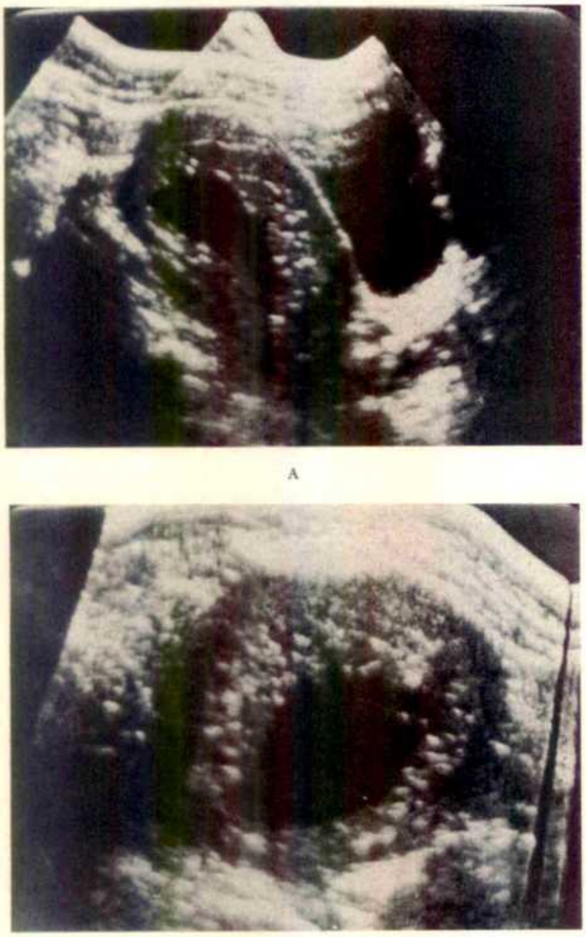
(Received December, 1976)

Ultrasound has greatly simplified the diagnosis of hydatidiform mole, which can usually be made with a high degree of reliability by the tenth week of amenorrhoea (Leopold and Asher, 1975). We would like to report a case with a particularly unusual and confusing scan.



A

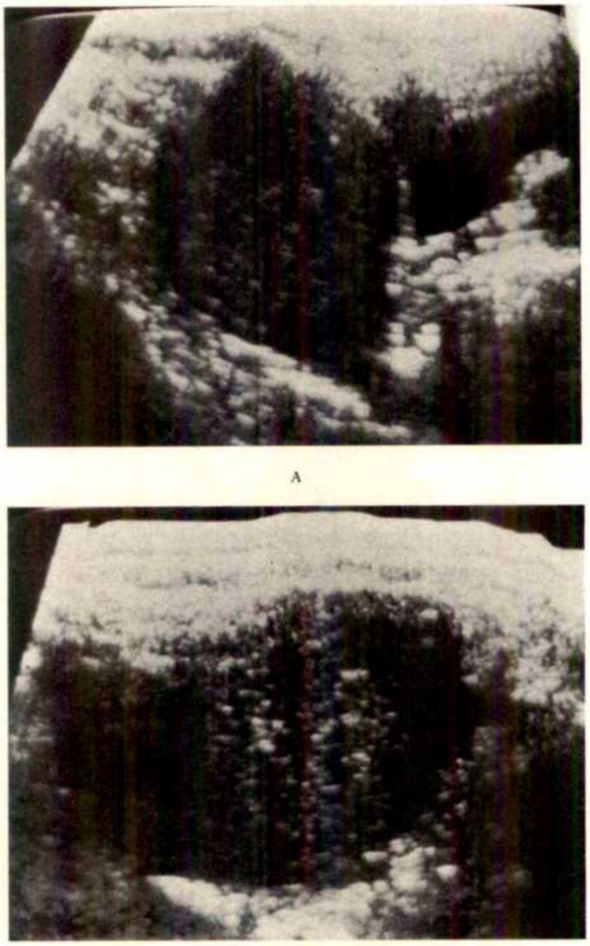
B

Fig. 1.

(A) Longitudinal mid-line B scan.
(B) Transverse scan.
There is a complete ring of low level echoes surrounding a central transonic space in the uterus.

Case History

A 23-year-old primipara presented at 11 weeks amenorrhoea with two recent episodes of vaginal bleeding. On clinical examination uterine size was consistent with dates. The pregnancy test was positive in normal dilution. Shortly following admission an ultrasound scan was performed (Fig. 1A and B). These scans appear to show a complete gestation ring, with a volume of approximately 60 ml, in which no fetus can be identified. A diagnosis of blighted ovum (anembryonic pregnancy) was therefore made (Robinson, 1975). A dilatation and curretage was carried out later the same day with evacuation of what looked like molar vesicles. Histological examination confirmed that this was a hydatidiform mole.



A

B

Fig. 2.

(A) Longitudinal mid-line B scan.
(B) Transverse scan.
The uterus is filled with a diffuse formless echo pattern. This is a proven case of hydatidiform mole at ten weeks amenorrhoea and shows the characteristic appearance at this stage.

Comment

The typical ultrasound appearance of a hydatidiform mole is of a uterus filled with a diffuse formless echo pattern ("snowstorm"), which disappears as the sound intensity is reduced. The multiple echoes arise from the myriad of fluid-filled vesicles within the uterus (Fig. 2A and B). It is not uncommon to find small clear spaces within this typical pattern due to the presence of unexpelled blood clot.

In retrospect the clue to the diagnosis is the conspicuous thickening and slight irregularity of the inner wall of the "sac". It seems probable that the central lucency was due to the large retained blood clot.

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1977, *British Journal of Radiology*, *50*, 445–446 JUNE 1977

Short communication

The effect of cimetidine on barium coating of the gastric mucosa

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(*Received October, 1976 and in revised form February, 1977*)

One of the problems in achieving high quality double contrast barium meal examinations is the variability of mucosal coating by barium sulphate suspensions. Improvement in coating may be achieved by improving the barium sulphate suspension itself (Miller, 1965; Embring and Mattsson, 1968), by increasing the duration of application of barium to the gastric wall with or without the use of anticholinergics and by ensuring complete cleanliness of the stomach. Ideally the stomach should be free of fluid to prevent dilution and flocculation of barium (Hunt and Anderson, 1976). Until recently, no effective and safe method of modifying the state of the gastric mucosa itself was available. Brimblecombe *et al.* (1975) described a new histamine H2 receptor antagonist, cimetidine, and studies by Pounder *et al.* (1975) have shown that cimetidine markedly decreased both the volume and acidity of gastric juice. No untoward side effects have been reported. It seemed that as well as its applications in the treatment of duodenal ulcer, the administration of cimetidine, by decreasing gastric secretion, might improve the mucosal coating properties of barium sulphate suspensions.

In this short communication we report the results of a trial designed to examine the effect of cimetidine on gastric mucosal coating by barium sulphate.

PATIENTS AND METHODS

Sixty male patients, aged 16 years or over, referred for barium meal examination, were randomly allocated to either cimetidine or matching placebo according to a prepared prescription list. The nature of the study was fully explained to each patient prior to entry and his consent obtained. Each patient received two tablets (400 mg) at 10 o'clock on the night before the examination and fasted overnight. Two tablets (400 mg) were taken one hour prior to the barium meal examination. No other medication was taken during the period of study. The barium sulphate suspension, gas tablets and X-ray equipment were identical for each examination. A standard series of radiographs was exposed during each patient examination. After completion of the trial the radiographs were read blind and independently by three observers who made a subjective assessment of the quality of the examination. Each observer scored as either "poor", "good", or "excellent": a) the quality of mucosal coating in the stomach including the quality of demonstration of the areae gastricae and b) the quality of mucosal coating in the duodenum. A consensus opinion was then arrived at for stomach and duodenum in each patient. Of the 60 patients randomly allocated to the trial, nine were not available for subsequent analysis due either to having failed to attend or to having an incomplete series of radiographs. Five of these were in the cimetidine group and four in the placebo group.

RESULTS

The consensus scores comparing the cimetidine and placebo groups are shown in Table I. The numbers involved are too small for statistical consideration but it can be seen that there is no difference between the study and control group according to the present investigation.

DISCUSSION

This study has shown no improvement in quality of mucosal coating after using cimetidine to diminish gastric secretion. It may be that mucosal coating is more dependent on the mucus component of gastric secretion than on the acid/fluid secretion. On a purely subjective basis there was a noticeable improvement in quality of coating in several patients with duodenal ulcer during treatment with cimetidine. Cimetidine may therefore be occasionally useful in the examination of patients with high acid output where mucosal coating is poor at an initial examination. Further investigation into drug techniques of modifying the gastric mucosa in the direction of improved coating is indicated.

ACKNOWLEDGMENTS

We wish to thank Smith Kline & French Laboratories, Welwyn Garden City, for supplies of cimetidine and Dr. G. P. Crean and his colleagues who referred the patients.

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TABLE I

QUALITY OF MUCOSAL COATING IN 51 PATIENTS (CONSENSUS OF THREE OBSERVERS)

	Stomach			Duodenum		
Technique	Excellent	Good	Poor	Excellent	Good	Poor
Cimetidine	7	11	7	4	14	7
Placebo	6	12	8	5	14	7

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Book review

Urologic Radiology. By M. L. Sussman and A. Newman, pp. xi+518, illus., 2nd edn, 1976 (Williams and Wilkins Co. Baltimore), £32.40.

This volume is the eighth of the 22 sections of Golden's Diagnostic Radiology series, and deals with the radiology of the urinary tract and suprarenal glands. The first text appeared in 1936 when it was hoped that by adding and replacing a few loose leaf pages it would be possible to maintain an up-to-date version. The rapid progress and expansion of urological radiology failed to justify this initial optimism and a new first edition was produced in 1967. The production of a second edition reflects the continuing developments within the subject. The text has been extensively revised with the techniques and relevance of the new methods of organ imaging and physiological measurement incorporated in the appropriate places.

The book includes 485 pages of text divided into 20 chapters dealing with methods of investigation, normal appearances, specific diseases and further more general accounts of the upper and lower urinary tracts. Emphasis has been placed upon the aetiology and pathology of the disease. The pathological basis of the radiological appearances and the contribution of radiology to the understanding of the aetiology and pathology are discussed in some detail. This edition thus provides an interesting background to the study of the urinary tract. The consequent pressure on space has meant that descriptions of the radiological findings, however, are often rather brief and superficial. There is a general dearth of information regarding the clinical presentations, and the differential diagnostic problems which may be posed in practice. Unfortunately, the text is often repetitive and at times contradictory. The authors offer a wide review of the opinions expressed in the literature but are unduly modest in their own views and leave the reader to make the final judgment. The subheadings are frequently at inappropriate sites and of unsuitable type settings. This makes the book difficult to use as a reference work and may intrude upon continuous reading. There are abundant illustrations which are in general well selected and are excellently reproduced. More than 700 references are provided in alphabetical order at the end of the volume. These represent a good cross section of the relevant literature and will facilitate a search through the original papers on any urological topic.

It is unlikely that this volume will be the first choice from textbooks on this subject but it will prove to be a valuable second source of information to radiologists with a special interest in the urinary tract and in the departmental library.

J. ROYLANCE.

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

THE USE OF HYOSCINE-N-BUTYLBROMIDE (BUSCOPAN)

In the light of an "epidemic" of intussusceptions, may we commend to your readers the use of hyoscine-N-butylbromide (Buscopan) in children. We have found that 4 mg in the infant by intramuscular injection facilitates retention of contrast enema by relaxing the bowel and feel that it has positively aided successful hydrostatic reductions. Standard texts do not mention pharmacological aids in such situations.

Yours, etc.,
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THE EDITOR—SIR,

SUBCUTANEOUS TOLERANCE OF CONTRAST MEDIA

Dr. Grech and Mr. L. Spitz (1977) report two cases of extensive subcutaneous necrosis following accidental injection of contrast medium into the fetus during amniography. In Case 1, 32 ml of Conray 280 and 5 ml Myodil were injected into the amniotic sac. In Case 2, 35 ml of Conray 280 was injected.

Dr. Grech kindly discussed Case 2 with me in 1970. I was so perturbed at the extent of subcutaneous necrosis of the arm in the infant, that I suggested to the manufacturers, May & Baker Ltd., the format of an animal investigation to investigate the subcutaneous tolerance of contrast media in *newborn* animals.

Mr. Brian Ingham, of May & Baker Ltd., conducted this investigation in 1970 with the following results.

Newborn rabbits were injected (0.5 ml subcutaneously into each shoulder) with Conray 280 (60% meglumine iothalamate) (280 mg iodine/ml) and Conray 420 (70% sodium iothalamate) diluted to contain 280 mg iodine/ml. In the 15 newborn rabbits, Conray 280 caused subcutaneous necrosis in eight animals, whereas diluted Conray 420 caused necrosis in only one animal. This suggests that the meglumine cation is much less well tolerated subcutaneously in the *newborn* rabbit than is the sodium ion.

Ingham also conducted a similar experiment injecting *mature* rabbits with Conray 280, Conray 420 (undiluted), Conray 420 (diluted to 270 mg iodine/ml), Hypaque 45% (270 mg Iodine/ml), Angiografin (methyl glucamine diatrizoate, 306 mg iodine/ml) and sterile saline. In all cases, each contrast medium was well tolerated without necrosis.

A similar experiment with a young *adult* dog also showed good tolerance to all the contrast media injected subcutaneously, except that undiluted Conray 420 produced a transient local oedema.

The deductions from Ingham's experiments are clear.

1. *Newborn* rabbits are much more sensitive to subcutaneous injection of contrast media than adult rabbits or adult dogs.
2. In *newborn* rabbits, the meglumine ion causes much more subcutaneous necrosis than the sodium ion.

The clinical implications are:

1. In the very rare instances where subcutaneous injections of contrast media need to be given, the sodium contrast media are much to be preferred to meglumine media. This is especially important in the newborn and infants. The contrast medium should not be of the concentrated variety.
2. For intra-uterine amniography, sodium contrast media are probably to be preferred to meglumine media. The only reservation is that if the injection by very rare accident is made into the skull or spinal canal, the sodium ion will be less well tolerated than the meglumine ion. Such an injection must be extremely rare, but Grech and Bevis (1969) reported a case in which the spinal subarachnoid space was injected with 2.5 ml Conray 280 during amniography.

A total intrauterine myelogram was produced. The infant was born unaffected. Follow-up examination eight years later revealed a normal child with no adverse sequelae.

Yours, etc.,
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THE EDITOR—SIR,

THE PERFORMANCE OF MULTI-ELEMENT BAND DISPLAYS IN RADIOISOTOPE IMAGING

The paper by Sharp and Mallard in the March 1976 issue of this journal was the latest of several publications purporting to show that the optimum conditions for radioisotope imaging employing a multi-level form of display is achieved when the range of count densities within each level is about three standard deviations of the mean. In general, this conclusion has been based upon consideration of simple test objects which do not adequately simulate clinical conditions.

Sharp and Mallard used the simplest situation of all, where a test object of one radioactive concentration is immersed in a bath of another concentration. Their claim that this represents a "clinically realistic test pattern" cannot be sustained. The example they quote of the central portion of a lateral brain scan is almost unique in that it does approximate to such a situation. Much more commonly, the count density varies in a complex manner over much of the area under investigation. It is to be anticipated that, if one disturbs the condition of uniform background, an abnormality would be required to produce a larger deviation from the mean in order to be recognized.

When the count density varies rapidly, an observer tends to register the shape of contours representing boundaries between adjacent levels, and clinical interpretation depends upon recognition of anomalies in these contours. This is a quite different situation to that considered by Sharp and Mallard. The requirements now are that the contours should be sharply defined and sufficiently close together that a small abnormality centred midway between two adjacent contours will not be missed. With the resolution currently available in radioisotope imaging, the minimum separation to satisfy the latter requirement is not less than about 0.5 cm. No additional information will be provided if the contours are spaced more closely than this, however many standard deviations separate them. On the contrary, they will begin to merge and definition will be lost. An extreme example of such a situation would be the display of a small but hyperactive thyroid gland, where a change from

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low count densities at its borders to very high count densities in the central region of the lobes may occur within about 1 cm. The optimum display in such circumstances will comprise only a very few contours separated by many standard deviations.

There is a further factor to be considered in multi-level displays. Consider, for example, an eight level display. Provided that an abnormality produces a count density change of more than about 12% of the total range displayed, a change in level must be triggered. The larger the number of standard deviations this represents, the better the definition of the level change in the display. Only when the count density change is smaller than this can the statistical fluctuations contribute to the detectability of an abnormality. For this reason, it is sometimes advantageous to utilize both a multi-level and a continuous display simultaneously, *e.g.* a colour scan and a photoscan, in such a way that they provide complementary information.

A separate issue raised by Sharp and Mallard is whether, when using a multi-level display, a "constant" or "statistical" band-width is to be preferred. A so-called "statistical ribbon" has sometimes been used for colour displays (Keyes and Gillespie, 1970) designed to give all the colour bands equal significance. This suffers from the severe limitation that the colour band-widths are only in the correct relationship if they are employed to cover the whole range of count densities from the maximum down to zero. Zero off-set or contrast enhancement cannot be employed without destroying that relationship. A method has been described (Dean, 1970) whereby a constant statistical relationship between count density and band-width is produced by the introduction of a "square rooting" circuit between the integrator and a constant band-width display mechanism. This system has the advantage that the desired statistical relationship is retained irrespective of the use of zero off-set and contrast enhancement. However, even this device is of limited practical value because the count density in clinical situations is rarely constant, and the definition of the contours in any multi-level display depends as much on the local count density gradients as on the counting statistics.

Yours, etc.,
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The Editor—Sir,

The Performance of Multi-Element Band Displays in Radioisotope Imaging

We would like to make the following comments on the letter by Sear (1977). One of the main problems in evaluating display performance is to produce a test-pattern which is simple to define and yet clinically realistic. One approach is to try to define certain characteristics of clinical images and to produce a test-pattern incorporating one or more of these features. The need to detect an abnormality in a region of rapidly changing count density, as on the edge of a liver; or in a region of uniform count density, as in the centre of the brain; are but two examples. In our study (Sharp and Mallard, 1976), we chose the latter pattern, firstly because it is simple to define and secondly because it is perhaps the easiest pattern in which to detect abnormalities. Therefore, we have the advantage that our results should give the lowest possible contrast at which it is possible to detect an abnormality of a particular shape and size. Thus we hope that our results provide a base-line showing the best possible display performance. This should provide one method, at least, of intercomparing display performances (Sharp, 1976).

Of course, it would be ridiculous to ignore clinical requirements when formulating such a test-pattern, no matter what the other advantages of the pattern might be. For example, we chose an abnormality 2 cm in diameter because we felt that was a reasonable representation of the smallest abnormalities regularly found in clinical practice.

We did not, however, claim that our test-pattern was "clinically realistic", but we were more cautious and claimed that it ". . . is not completely divorced from having any clinical meaning . . .". Clinical images have been used in work by Schulz *et al.* (1970) and Houston (1976), and interesting and valuable though this work is it can still be criticized as producing results which are relevant only in relation to the particular organ which the investigators chose to use.

We agree with Dr. Sear's suggestion that investigations should be made with other types of test-patterns and we see our work as only just starting. So far this work has measured image contrast as a function of background count density, but there is a need to use parameters which have more physical meaning such as concentration ratio, collimator response, scanning time, etc. Also, the problem of locating the abnormality has only been investigated as one of detection, *i.e.* the observer only has to say that something abnormal is present; but there is also the problem of recognition of the abnormality, by giving an accurate estimate of its size and shape. These are just a few of the many problems still remaining.

In our work we used a popular type of display in which the image is formed on a matrix, each element of which represents some pre-determined area of the image, in our case a region 5 mm square. Our interest was in deciding how to assign one of eight available grey shades to the count density associated with each element. The minimum distance between our "contour lines" is therefore 5 mm and we cannot vary it. We know of no convincing experimental evidence about the optimum element size for various clinical investigations, but with regard to Dr. Sear's example of the image of a small hyperactive thyroid we can only suggest that if he sees fit to image it with a small element size then he must also consider it worthwhile to display it at the same element size.

The comment that Dr. Sear makes about the "statistical ribbon" appears to depend upon the type of display system used and we do not think it that constitutes a valid general criticism of the use of statistical levels to optimize the display.

There is no doubt that the investigation of display performance is extremely complex, involving, as it does, not only the display itself but the observer. It is necessary, therefore, for the problem to be tackled by different groups using different methods; for example, we use constant stimuli whilst others use receiver operating characteristic (ROC) curves. The number of individual questions to be answered is very large and it is unlikely that they will all be solved in the authors' lifetimes!

Yours, etc.,
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J. R. Mallard.

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THE EDITOR—SIR,

SKIN-SPARING WITH D-T NEUTRONS

The build-up region of the depth dose distribution for a neutron beam produced by the d-T reaction was a topic of interest at the recent conference (Particles and Radiation Therapy, II) held in Berkeley, California. Dosimetry measurements (Greene and Thomas, 1968; Rossi, 1971; Smathers and Almond, 1976) have indicated that the entrance dose for a d-T neutron beam is about 70% of the dose at maximum build-up. For a neutron beam produced by 50 MeV deuterons on beryllium the corresponding dose is 40% (Smathers and Almond, 1976).

Subsequent to the conference, build-up measurements for a d-T neutron beam were made using an extrapolation ionization chamber, at the ICT facility of the Lawrence Livermore Laboratory. The object of this work was to discover the cause of the relatively high entrance dose and to find means of reducing it.

The tables summarize the results of these measurements. As is evident from the data, skin-sparing with d-T neutrons can be readily achieved. By using a thin sheet of lead to cover the target and a similar sheet to cover the collimator exit portal, the relative entrance dose was reduced to 38%. Further reduction of this dose is possible by placing lead at the skin surface, but with some added inconvenience.

Possible causes of the high entrance dose are low energy photons and/or charged particles (generated in the target assembly, the collimator and the air column between the target and detector), which subsequently reach the detector. Further work with various thicknesses of lead is necessary to further define the nature of the unwanted radiation.

Yours, etc.,
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TABLE I

NO COLLIMATOR: SSD = 50 CM

Thickness of Pb on target (mm)	0	0.89	1.73
Relative entrance dose	63%*	48%	46%

*By placing 1.02 mm of mylar on the target, the entrance dose was increased by about 6%.

SSD = Source-skin distance.

TABLE II

NO COLLIMATOR: SSD = 100 CM (PB "TENT" OVER DETECTOR, OPEN TOWARDS TARGET)

Thickness of Pb on target (mm)	0	0.91
Relative entrance dose	53%	44%

SSD = Source-skin distance.

TABLE III

WITH COLLIMATOR*: SSD = 100 CM (PB "TENT" OVER DETECTOR, OPEN TOWARD TARGET)

Thickness of Pb on target (mm)	0.91	0.91	0.91
Thickness of Pb over collimator exit	0	0.46	0.91
Relative entrance dose	52%	38%	38%†

*Collimator, 76 cm long; exit face, 9 cm from detector; exit portal, 7.5 cm × 7.5 cm.

†Moving collimator toward target by 9 cm increased entrance dose from 38% to 39%.

SSD = Source-skin distance.

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THE EDITOR—SIR,

SECONDARY RADIATION FROM SUPERVOLTAGE ACCELERATORS —ITS IMPLICATIONS IN PATIENT PROTECTION

If the collimator and compensator of a supervoltage accelerator are made of high atomic number material they will tend to interact with the high energy photon beam predominantly by pair-production. Associated with pair-production is a cascade formation resulting in a variety of radiations. *i.e.* pair-electrons, annihilation radiation, bremsstrahlung, Compton scattered photons and recoil electrons. All of these radiations (hereafter referred to as the Secondary Radiation Originating in the Collimator-Compensator, abbreviated as "SROCC") may reach a phantom and significantly contribute to the dose up to several centimetres deep (Bhatnagar and Spira, 1975). "SROCC" is basically an uncollimated radiation and soft in nature. The intensity of "SROCC" decreases with increasing depth in a phantom due to attenuation and increasing distance from the collimator-compensator.

The implications of "SROCC", which is outside the useful beam, may be serious from the point of view of patient protection, especially if the field of treatment is located close to some superficially located critical organ. For example, we measured gonadal doses on a young male patient undergoing treatment of the prostate by a 42 MV X-ray beam from a Siemen's betatron. (The collimator and compensator of this betatron are made of lead. The collimator is of the "single-plane" type (Johns and Cunningham 1969) and compensator number 2 is conical in shape with a height of 2.5 cm and base diameter 7.0 cm. The collimator and compensator are located at a distance of approximately 60 cm from the target, and treatments are usually carried out at 120 cm TSD.) A dose of 200 rad was planned at the mid-depth (10 cm) by an anterior field of 15 cm × 15 cm. The inferior edge of the field was 3.5 cm above the scrotum. A set of three TLD micro-rods (CaF2: Mn) with 1 cm build-up to approximate the average depth of the gonads was placed over the testicles during the treatment. The gonads were found to be receiving about 15% of the mid-depth dose. When a lead block 1.5 cm thick was placed over the patient's thighs covering the scrotum, the gonadal dose was reduced to less than 2% of the mid-depth dose. Obviously, the radiation reaching the gonads could not be due to tissue scatter.

A similar set of measurements was then repeated on a specially constructed scrotum-penis phantom made out of dental wax and attached to a Rando-phantom. The pelvic treatment field (15 cm × 15 cm) was marked on the Rando-phantom. A hole to take a Shonka-probe (volume 0.05 cm^3) was drilled in the scrotum parallel to the field-edge at 3.5 cm distance and at 1 cm depth below the surface in a position which represented the centre of the gonads. A dose of 200 rad was delivered to the mid-depth of the phantom (d = 10.5 cm). The Shonka-probe recorded a dose of about 15% of the mid-depth dose. When the lead block 1.5 cm thick was placed in a manner similar to that done for the patient the Shonka-probe recorded only 1.8% of the mid-depth dose.

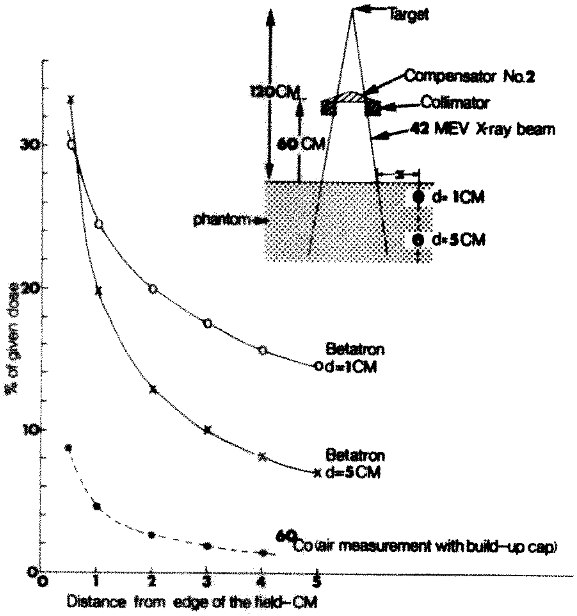

FIG. 1.

Doses outside the primary beams of 42 MV X-rays and cobalt 60 γ-rays. Doses for the 42 MV X-ray beam were measured in a polystyrene phantom at depths of 1 cm and 5 cm. The experimental arrangement is shown in the insert. Doses for the cobalt 60 γ-ray beam were measured in air with the cobalt build-up cap at 80 cm source-to-chamber distance. A Shonka ion-chamber with 0.05 cm^3 volume was used in these measurements.

It was further found that when the lead block was placed away from the phantom on the block-holding tray, it was not as effective in shielding the gonads as before. Thus, the lead block must be placed close to the critical organ to be protected.

Figure 1 shows the results of an experiment designed to measure the doses outside the primary field as a function of distance from the edge of the field, at depths of 1 cm and 5 cm in a polystyrene phantom. The experimental set-up is shown in the insert of this figure. The same Shonka-probe as used earlier was used in this experiment. For comparison purpose, the doses measured outside the γ-ray beam (15 cm × 15 cm) from a cobalt 60 unit, in air with cobalt 60 build-up cap on the Shonka-probe, are also given in Fig. 1. Strangely enough, it is seen that the doses outside the cobalt 60 beam are far smaller than the doses outside the 42 MeV X-ray beam from a Siemen's betatron.

In view of our measurements, the following suggestions are made to those institutions using a Siemen's 42 MeV betatron or in general to any institution using a super-voltage accelerator where high-atomic number materials are used in the construction of the compensator and collimator and especially where the compensator may be located rather close to the patient's skin:

1. Because "SROCC" may result in fairly high doses to critical organs outside the field, such as to the lens of the eyes while treating head and neck tumours as well as to the gonads in treating bladder and prostatic tumours, an effort must be made to reduce the dose to these organs to avoid cataract formation and to reduce genetic hazard respectively.
2. Shielding of critical organs can be acccomplished by covering them with a 1.5 cm thick lead block. Eyes can be shielded by covering them with a curved block of 1.5 cm thickness resting on zygomatic, frontal and nasal bones.
3. The shielding block must be placed close to the organ. When the same block is placed away from the organ, on the shadow-tray, its effectiveness in shielding is considerably reduced.

Yours, etc.
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1977, *British Journal of Radiology*, *50*, 451–456 JUNE 1977

Proceedings of The British Institute of Radiology

Whole body counting and scanning

Abstracts of papers read at a meeting arranged by the Nuclear Medicine Committee, The British Institute of Radiology, on Wednesday, November 24, 1976, at the Reid-Knox Hall, 32 Welbeck Street, London W1M 7PG

Chairman: Dr. D. J. Keeling

Dynamic radioisotope studies using a high sensitivity whole body counter, by R. Hesp, J. Reeve, T. Smith, R. Wootton, and N. Veall.

The measurement of total body potassium in a study of post-prostatectomy irrigation, by T. Hawkins, A. W. Goode, and J. G. W. Feggetter.

New body-monitoring facilities at the NRPB, by A. Knight.

Rapporteur Session, by N. G. Trott.

Whole-body counters: are they valuable clinical tools or status symbols? by K. Boddy.*

Clinical experience of measuring total body potassium, by K. Boddy.*

Investigations into some physical and anatomical factors affecting the accuracy of whole-body counting, by P. Tothill.*

Development and applications of a low background whole-body scanner with digital output, by N. G. Trott, Sarah Milan, Adele Nicholas, Mary E. A. O'Connell, and Heather A. Steere.*

Quantitative whole-body scanning and regional uptake using the hybrid scanner, by J. C. W. Crawley and G. P. Gibbs.*

The use of a whole-body monitor for the study of Zinc-65 metabolism in patients with dermatological disease, by T. Hawkins, Janet Marks, Valerie M. Plummer, and M. W. Greaves.*

Assessment of rheumatoid inflammation in the knee joint using ^{99}Tc^{m} pertechnetate profile scanning, by W. S. Watson and J. Paterson.*

Clinical applications of the Birmingham whole-body counter using the *in vivo* neutron activation system, by Helen M. James, D. R. Chettle, and J. Dabek.

The accuracy of absolute determination of total body calcium, by T. J. Spinks, D. K. Bewley, and A. S. O. Ranicar.

A direct comparison of two methods of measuring total body nitrogen by *in vivo* neutron activation analysis, by C. B. Oxby, I. McCarthy, and L. Burkinshaw.

Clinical experience of measuring gastrointestinal absorption and retention using whole-body counters and long term balance by *in vivo* activation analysis, by K. Boddy.

The use of whole-body counting and profile scanning in turnover studies of some radiopharmaceuticals, by P. Tothill, M. A. Smith, J. D. Simpson, J. N. Macpherson, and M. V. Merrick.

^{52}Fe studies of bone marrow depression and regeneration following large field radiotherapy, by S. C. Lillicrap, Heather A. Steere, H. M. Clink, and M. J. Peckham.

The measurement of the rate of blood loss using Iron-59 and whole-body counting, by G. M. Owen, W. H. Thomson, J. A. F. Napier, and A. Jacobs.

*Covered in Rapporteur Session.

DYNAMIC RADIOISOTOPE STUDIES USING A HIGH SENSITIVITY WHOLE-BODY COUNTER

By R. Hesp, J. Reeve, T. Smith, R. Wootton and N. Veall

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The most important use of radioactive tracers is in the study of the dynamic metabolic processes which characterize all living organisms. The term "dynamic studies" is commonly associated with those processes where the tracer has a mean transit time measured in seconds or minutes. There are many equally important processes with transit times measured in months or years. Their study necessitates the use of long-lived tracers and hence of low administered dose levels. The high sensitivity whole-body counter is an essential tool for this type of study, but its possibilities have been largely neglected.

An immediately obvious application is the use of ^{47}Ca and ^{85}Sr for work on bone mineral metabolism. Marshall's formula permits the derivation of the plasma specific activity—time function from the whole-body counting and excretion rate data. This can be deconvoluted from the whole-body retention function to eliminate the effects of re-utilization of the tracer. It then becomes possible to estimate the parameters which determine bone formation and resorption rates by conventional methods.

The results obtained in calcium metabolic studies indicate that the high sensitivity whole-body counter is generally applicable in any situation where the long-term retention of the tracer is restricted to a particular organ or metabolic pool.

THE MEASUREMENT OF TOTAL BODY POTASSIUM IN A STUDY OF POST-PROSTATECTOMY IRRIGATION

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The retention of blood clots is one of the most important post-operative difficulties following prostatectomy. The management of such patients either by conventional irrigation or the use of diuretics is well established—both of which seek to provide a free flow of urine to wash out the bladder. The use of the diuretic Mannitol has been associated with a significant loss of potassium—a loss which could be of some consequence to the elderly patient.

Following prostatectomy a small loss of lean body mass, and hence potassium, is expected from the obligatory metabolic response to trauma. A further small loss of total body potassium (TBK) may follow from cellular depletion as a consequence of acid base changes. We have investigated the possibility of an increased potassium loss following administration of the more powerful diuretic Lasix. Twenty patients were randomly allocated to either the Diuretic group or the conventional Irrigation group. Total body potassium (TBK) was measured pre- and post-operatively and the results compared. Measurements of TBK were made using a shadow-shield monitor, previously calibrated to allow rapid serial measurements.

Results indicated a small net loss of TBK in both groups with the Diuretic group (104 mmol K) being slightly greater than the Irrigation group (32 mmol K). The difference was not significant ($0.1 > P > 0.05$). It is concluded that Lasix, used as a post-operative method of irrigation, is not a further potent cause of potassium loss in the prostatectomy patient.

NEW BODY-MONITORING FACILITIES AT THE NRPB

By A. Knight

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A description was given of the new NRPB body monitoring facilities which include a whole-body monitor, a low-energy photon monitor, and associated electronic and data-processing equipment.

Careful selection procedures for the laboratory construction materials ensure low site background. The effect of the main steel shield is documented in terms of Background Index.

Details were provided of the whole-body monitor, a six-crystal ring around a moving bed. The low-energy photon monitor, an array of four dual-crystal detectors used mainly for determining transuranic nuclides in lungs, was also described along with the pulse-shape analysis technique for background reduction. Calibration procedures for both monitors were presented, highlighting special difficulties such as subject background and tissue attenuation with incorporated nuclides that emit low-energy photons. A project to develop a realistic chest phantom consisting of a thoracic cage with tissue- and lung-equivalent material was described.

An account was provided of the control data-processing system which uses CAMAC and a small computer and to which several other spectrometric detectors are input.

Performance data including the results of recent measurements were discussed and an outline of future work was given.

RAPPORTEUR SESSION

By N. G. Trott

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The final programme was assembled from the papers submitted to represent as fully as possible the range of work in progress in the United Kingdom and the institutions involved in the field. However, in order to leave sufficient time for questions and discussions seven of the submitted papers (marked *) were not presented in full but reviewed in this rapporteur session.

WHOLE-BODY COUNTERS—ARE THEY VALUABLE CLINICAL TOOLS OR STATUS SYMBOLS?*

By K. Boddy

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Whole-body counters and their clinical usefulness were evaluated in four respects: (a) their unique capabilities; (b) in comparison with other clinical tests intended to provide analogous information; (c) patient amenity and comfort; (d) economic factors. It is suggested that the capability of measuring directly total body potassium and the oral absorption and retention of specific administered radioisotopes or labelled compounds on an outpatient basis is particularly valuable. Competitive methods of direct measurement generally involve excreta collection and assay which is notoriously inaccurate and inconvenient while indirect methods are often influenced by concomitant clinical disorders. Whole-body counting measurements generally involve little or no discomfort to the patient who also, in our experience, usually prefers examination as an out-patient. An assessment of the economic aspects of whole-body counters was given with respect to the type of counter to be used but, particularly, in comparing the capital and operating costs of whole-body counters with alternative tests for which hospitalization of the patient is required. It is concluded that whole-body counters have economic advantages as well as superiority in accuracy, reliability and convenience. A possible explanation of and a remedy for the under-utilization of some whole-body counters was offered.

CLINICAL EXPERIENCE OF MEASURING TOTAL BODY POTASSIUM*

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The direct measurement of total body potassium (TBK) by whole-body counting of ^{40}K was compared and contrasted with the indirect methods in current clinical use. Problems in the clinical interpretation of TBK, with particular reference to "normal" values, were discussed. Application of the method in renal disease, cor pulmonale, diabetes mellitus, rheumatoid arthritis, childhood coeliac disease, patients with uretero-sigmoid anastomoses and "ultra-fit" subjects were presented together with the influence of treatment of the diseases.

INVESTIGATIONS INTO SOME PHYSICAL AND ANATOMICAL FACTORS AFFECTING THE ACCURACY OF WHOLE BODY COUNTING*

By P. Tothill

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Dudley and ben Haim (1968) demonstrated the value of a scanning geometry in whole-body counting, together with the advantages of bilateral counting and the inclusion of Compton scattered radiation in the energy range accepted to minimize changes of counting efficiency with re-distribution of radionuclide within the body. We have extended their work to lower energies and examined phantoms of different thicknesses. The conclusion remains that, over considerable ranges of size and energy, counting in a wide energy band leads to a good independence of counting efficiency upon source depth. Patient measurements showed how accurately an absolute determination of whole-body activity could be made; for higher energy gamma emitters the accuracy was surprisingly good.

Bilateral detection can be obtained with a single detector by making measurements with the patient alternately prone and supine. Investigations were carried out on subjects after ^{58}Co cyanocobalamin ingestion to determine whether such patient rotation led to "organ flop", movements of activity relative to the anterior and posterior surfaces of the body, which would detract from the accuracy of the technique. No significant movements were found to take place.

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DEVELOPMENT AND APPLICATIONS OF A LOW BACKGROUND WHOLE-BODY SCANNER WITH DIGITAL OUTPUT*

By N. G. Trott, Sarah Milan, Adele Nicholas, Mary E. A. O'Connell and Heather A. Steere

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A dual detector whole-body scanner, with a number of features not generally available on commercially produced instruments, was developed by Cottrall *et al.* (1973) and has been in clinical use at this hospital for about five years. It incorporates two heavily shielded 12.5 cm diameter × 5 cm thick NaI(Tl) detectors, with a couch driven at a widely variable range of speeds and displacements over rectangular co-ordinates up to 182 cm × 82 cm, and is set up in a low background laboratory. The positions of the detectors relative to each other and to their shields can be readily adjusted, and patients can be accurately re-positioned. To provide data on the position of the couch an optical encoder mounted on the drive shaft provides pulses at 0.3 mm intervals. There is no direct display system; count and position data are stored in the core of a multi-channel analyser used as a multiscaler (now Nuclear Data ND 812) formerly Intertechnique SA 40) and processed via a data link to the University of London CDC 7600 Computer.

The system has proved very flexible and has been applied to a considerable range of clinical problems as well as for radionuclide dosimetry. At one extreme it has been used for sequential scanning, over periods of days or weeks on patients to whom only 10 μCi ^{59}Fe or 100 μCi ^{51}Cr had been administered for haematological investigations, quite coarse collimation being provided to give a measure of the total counts recorded over a given length of travel. From the digital record, total counts over selected areas corresponding to the sites of particular organs such as the lungs or heart can be determined and hence the variation of uptake with time in those sites evaluated. A similar approach, using multi-hole focusing collimators, has been used in following the turnover of ^{32}P/^{131}I Lipiodol in patients receiving intralymphatic therapy (O'Connell *et al.*, 1976). Recently (as described fully in another paper at this meeting) distribution of bone marrow in certain patients has been investigated (Lillicrap *et al.*, 1976).

This report was concerned chiefly with the development and study of collimators, of methods of displaying data and of procedures used in defining the boundaries of organs. Line spread and modulation transfer functions, as well as the sensitivity, have been evaluated for the various collimators used. Display systems have evolved from isocount lines to a type of grey scale image incorporating numeric symbols and most recently a microfilm presentation. These modes of presentation can be varied to suit the type of study.

Direct recording on to a core store has proved very successful and in our experience far less trouble than some alternative techniques such as paper tape recording from a buffer store. Although mini-computers could be used for some of the data processing, in practice there have been considerable advantages in having available all the programming capability of the London University computer.

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Lillicrap, S. C., Steere, H. A., and Clink, H. M., 1976. Distributions and dosimetry of ^{52}Fe and ^{59}Fe in bone marrow and other organs. In *Radioaktive Isotope in Klinik und Forschung*, *12*, pp. 79–80 (Egerman, Vienna).

QUANTITATIVE WHOLE-BODY SCANNING AND REGIONAL UPTAKE USING THE HYBRID SCANNER*

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The hybrid scanner (Crawley and Veall, 1973) consists of two line detectors, one above and one below a moving couch. The detectors give signals corresponding to γ rays originating along a line normal to the direction of the couch. In the present version of the instrument, holes in an opaque strip mounted along the side of the couch allow light to reach a detector and to give signals corresponding to the position of the couch. Each pulse of light causes the distribution across the couch for 2 cm of longitudinal scan to be recorded on digital magnetic tape which is taken to an off-line computer. Scans are corrected for non-linearity and non-uniformity of sensitivity and top and bottom scans are combined to reduce the depth dependence. Areas selected from a line printer display with ten grey levels can be integrated. Scans can be repeated at intervals of three minutes, so dynamic studies characterized by transit times of minutes or hours are possible.

The instrument is in use for clinical studies including regional bone blood flow using a modification of the technique of Wootton *et al.* (1976) and the distribution of liposomes carrying radioactive tracers. The quantitative hybrid scanner is particularly useful when relatively slow changes in distribution are expected, but where there is no *a priori* reason for expecting concentration in a particular region of the body.

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Proceedings of The British Institute of Radiology

THE USE OF A WHOLE-BODY MONITOR FOR THE STUDY OF ZINC-65 METABOLISM IN PATIENTS WITH DERMATOLOGICAL DISEASES*

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There has been much work on zinc and its distribution in the body, though with relatively few studies related to the skin and its diseases. Serum zinc concentration has been shown to be abnormally low in certain dermatological conditions but this has not correlated well with skin zinc content.

Using a whole-body monitor we have studied some patients with skin disorders regardless of their serum zinc levels, in an attempt to identify an abnormality of ^{65}Zn metabolism. The whole body retention of ^{65}Zn has been measured for a period of up to one year following oral administration. The retention was compared with indirect assessment from urine and faecal loss. Data from the few reports of ^{65}Zn kinetics in apparently healthy subjects have been used for comparison (Hawkins *et al.*, 1976).

For the group as a whole, the percentage retention and the long term biological half time showed wide variation. The mean values were 61% and 399 days respectively, similar to values of the normals. It was observed that for patients with venous leg ulcers taken as a clinical sub-group, the mean values of retention and half time were smaller than the remaining population/(48% and 71%; 329 and 451 days); the latter was significant at $P=0.04$. Except for this interesting finding no clear abnormality of ^{65}Zn metabolism was identified. Use of the monitor for crude localization studies in three patients indicated a single region of high activity in the mid-thorax. A high initial uptake by the liver was confirmed by rectilinear scanning.

REFERENCE

Hawkins, T., Marks, J., Plummer, V. M., and Greaves, M. W., 1976. Whole-body monitoring and other studies of zinc 65 metabolism in patients with dermatological disease. *Clinical and Experimental Dermatology*, *1*, 243–252.

ASSESSMENT OF RHEUMATOID INFLAMMATION IN THE KNEE JOINT USING ^{99}Tc^{m} PERTECHNETATE PROFILE SCANNING*

By W. S. Watson and J. Paterson

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In the last few years, the increased uptake of ^{99}Tc^{m} pertechnetate by inflamed tissue has been used as a measure of rheumatoid inflammation in several joints including the knees. In general the methods previously used involved a single fixed detector positioned over the joint and the count rate obtained was normalized by counting an aliquot of the injected dose.

In the present study, a six-detector whole-body monitor was used in profile scanning mode to measure knee uptake of ^{99}Tc^{m} and also to allow direct normalization of the knee count rate since whole body ^{99}Tc^{m} activity is simultaneously measured during the profile scan.

The detectors are connected in vertically opposed pairs giving three activity profiles, from head to foot, of different transverse sections of the body, *i.e.* two lateral profiles and one mid-line profile. The sum of the three count rates gives a measure of whole body activity while the peak count rate over the knees is obtainable from the lateral profiles. The normalized ^{99}Tc^{m} uptake in the knee (NTU) is given by

$$\text{NTU}=\frac{100\ \text{(peak count rate over knee)}}{\text{Average whole body count rate}}$$

A correction factor for the varying degree of body tissue absorption of the ^{99}Tc^{m} γ rays was used to eliminate the effects of differing body weight. This factor, obtained using water-filled polythene phantoms of varying height and weight, is independent of height and linearly related to $\sqrt{\text{(Body Weight)}}$.

The technique has been employed initially to measure the effect of intra-articular steroid injection into the knee joint. Ten patients with either unilateral or bilateral rheumatoid involvement in the knee were studied. Whole body profile scans were obtained 15 to 20 minutes after intravenous injection of 100 μCi ^{99}Tc^{m}-pertechnetate, immediately prior to steroid injection and also three, seven and 14 days later.

Latreal profile scans on a patient with unilateral involvement were taken immediately before steroid therapy and then three and 14 days later. Pre-treatment asymmetry of knee uptake was clearly demonstrated on the Day 0 profiles and the response to therapy was in evidence on both Day 3 and Day 14. The mean NTU values for the treated group on Days 3, 7 and 14 were significantly different from the pre-treatment Day 0 value while the mean NTU value for the untreated group did not vary significantly during the 14-day period.

On each day the patients were studied, other assessment parameters were also recorded: these included a subjective pain score estimated by the patient, a clinically assessed index of inflammation, and knee temperature differences obtained by both infra-red thermography and thermistor techniques. The group mean values of these parameters for the treated knee group were not, in general, as significantly different from pre-treatment values as was the mean NTU. On at least one day, usually Day 14, all these parameters apart from the NTU showed non-significant pre-post treatment differences.

In addition to studying the variation of the group mean values, correlations were sought between the parameters obtained; the correlation between NTU and pain score was significant at the 99% level. The internal consistency of the study was evidenced by the close agreement between the predicted NTU for pain=0, *i.e.* NTU=23.6, and the mean value for the untreated asymptomatic knees, *i.e.* NTU=23.8.

This study indicates that the measurement of ^{99}Tc^{m} uptake in rheumatoid joints is a practical way of grading the degree of rheumatoid involvement and, prehaps more important, provides a useful tool for the objective assessment of anti-inflammatory drug therapy.

Proceedings of The British Institute of Radiology

CLINICAL APPLICATIONS OF THE BIRMINGHAM WHOLE-BODY COUNTER AND THE *IN VIVO* NEUTRON ACTIVATION TECHNIQUE

By H. M. James

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Because of the proximity of the *in vivo* neutron activation facility at the University of Birmingham Nuffield Cyclotron, we have been able to extend the variety of clinical applications of the whole-body counter by activating some important elements and measuring their content in the body. Patients are referred by clinicians from several major hospitals in the vicinity of the university for measurements of whole-body potassium, absorption and turnover of radioactive tracers, and for measurements which involve *in vivo* neutron activation.

Some investigations of clinical value which involve neutron activation are: whole body calcium in the progress and treatment of disorders such as chronic renal failure, malabsorption, osteoporosis, thyrotoxicosis and hyperparathyroidism; whole-body sodium in hypertension; liver copper in Wilson's disease; liver iron in haemosiderosis; estimation of potassium depletion using whole body nitrogen. These procedures are found acceptable by the patients, and the *in vivo* activation involving whole-body neutron doses between 0.1 and 1 rem has been approved by the Medical Ethical Committees.

THE ACCURACY OF ABSOLUTE DETERMINATION OF TOTAL BODY CALCIUM

By J. T. Spinks, D. K. Bewley, and A. S. O. Ranicar

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The technique of *in vivo* neutron activation has been used by several centres over the past decade in the measurement of the elemental composition of the human body, particularly the determination of changes in Ca content in bone disease. The irregular shape of the body and the irregular distribution of Ca within the body makes absolute quantitation relatively difficult. However, if Ca mass could be assessed with reasonable accuracy, a single measurement would reveal how far body content deviated from normal.

Our method of body Ca determination employs bilateral irradiation with a cyclotron-produced fast neutron beam of mean energy 7.5 MeV, followed by counting in a sensitive whole body monitor. The use of two phantoms, of sizes covering approximately the range of patient sizes encountered, allowed us to determine the effects of body dimensions on efficiency of activation and counting. A skeleton-like structure was also built into one of the phantoms enabling us to assess the effects of non-uniformity of element distribution.

It is estimated that random errors amount to 8% (2 s.d.) and that the combined systematic error is also about 8%.

A DIRECT COMPARISON OF TWO METHODS OF MEASURING TOTAL BODY NITROGEN BY *IN VIVO* NEUTRON ACTIVATION ANALYSIS

By C. B. Oxby, I. McCarthy, and L. Burkinshaw

Department of Medical Physics, University of Leeds

The nitrogen content of the body can be estimated by irradiating with fast neutrons and measuring either the prompt γ rays emitted in the slow neutron reaction ^{14}N(n, γ)^{15}N or the radioactivity induced by the fast neutron reaction ^{14}N(n, 2n)^{13}N. The latter technique also gives estimates of potassium, phosphorus, sodium, chlorine and calcium. Both methods are being developed at Leeds, using continuous irradiation with 14 MeV neutrons.

The induced activity method has been compared directly with the prompt γ-ray method as implemented at the University of Birmingham, where a pulsed beam of neutrons with a mean energy of approximately 3 MeV is used. Five healthy men were measured at the two centres, with a maximum interval of five days between measurements. The results were discussed principally in terms of problems encountered in calibrating the Leeds installation; interrelationships between the estimates of various elements were also considered.

CLINICAL EXPERIENCE OF MEASURING GASTROINTESTINAL ABSORPTION AND RETENTION USING WHOLE-BODY COUNTERS AND LONG TERM BALANCE BY *IN VIVO* ACTIVATION ANALYSIS

By K. Boddy

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The MERLIN mobile and installed shadow-shield whole-body counters have been used in a wide variety of clinical studies to measure gastrointestinal absorption and long-term retention of administered radioisotopes, especially ^{59}Fe and labelled vitamin B_{12}. The oral absorption of 5 mg iron has been measured in healthy males (1.2–21.5%, mean 9.6±0.9%) and females 0.8–23.7%, mean 11.4±2.2%), in iron deficient patients (14.1–64.0%, mean 39.1±5.5%), in pernicious anaemia (2.1–38.4%, mean 12.4±3.3%) and rheumatoid arthritis (1.6–41.8%, mean 14.2±2.7%). In chronic renal failure, oral absorption, long term retention and iron incorporation into erythrocytes were measured simultaneously in non-dialysed patients, patients receiving renal dialysis treatment and following renal transplantation. The results are summarized in Table I.

Oral absorption of vitamin B_{12}, without and with intrinsic factor (IF), were measured in double tracer tests with ^{58}Co-vitamin B_{12} alone and ^{57}Co-vitamin B_{12} with IF, usually administered on the same day. In control subjects, the absorption of vitamin B_{12} alone ranged from 26 to 63% (mean 41%) and the ratio of B_{12}+IF)/B_{12} was less than two in all subjects. In patients with pernicious anaemia the absorption of vitamin B_{12} alone ranged from 1.8 to 11.4% (mean 7.1%) and the ratio of (B_{12}+IF)/B_{12} was less than two in each case. Factors influencing the absorption of vitamin B_{12} were studied using a similar approach while measurement of the long-term retention of parenterally administered vitamin B_{12} analogues, in therapeutic doses, established a scientific and quantitative basis for therapy schedules.

Analogous methods have been used to measure the absorption of calcium, zinc, and, most recently, magnesium in a study of its metabolism with respect to coronary heart disease.

The installed whole-body counter is currently used primarily in long-term balance studies in which the total body content of calcium, phosphorus, sodium, chlorine, nitrogen and potassium are measured by *in vivo* neutron activation analysis in conditions such as hypertension, rheumatoid arthritis and renal failure.

TABLE I

Summary of data on iron metabolism. Mean values are quoted with the standard error of the mean in parentheses

Subjects	Absorption of oral ^{59}Fe (%)	^{59}Fe incorporation into erythrocytes (%)	Rate of loss of ^{59}Fe from body (%/day)
Normal subjects	10.0 (0.85)	81.0 (1.4)	0.15 (0.04)
Patients with functioning renal homografts	5.09 (2.07)	61.1 (7.0)	0.10 (0.01)
Non-dialysed patients with chronic renal failure	3.47 (0.90)	45.0 (6.0)	0.18 (0.04)
Patients with chronic renal failure receiving regular dialysis treatment	2.0 (0.47)	23.8 (4.3)	0.53 (0.07)

THE USE OF WHOLE-BODY COUNTING AND PROFILE SCANNING IN TURNOVER STUDIES OF SOME RADIOPHARMACEUTICALS

By P. Tothill, M. A. Smith, J. D. Simpson, J. N. Macpherson and M. V. Merrick

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Royal Infirmary and Western General Hospital, Edinburgh

Whole-body counting provides the highest sensitivity for turnover studies, but no positional information. Profile scanning gives the latter in one dimension with a sensitivity about ten times that of two dimensional scanning and with simpler quantitation. We have used these characteristics to make dynamic studies with time scales ranging from minutes to months. The former are exemplified by measurements of the rate of liver uptake of colloid and the rate of absorption of radioiodine. As an example of long term studies, we have followed the retention of ^{85}Sr, both whole- and part-body, for periods up to five months. The effect of calcitonin treatment in patients with Paget's disease has been studied; changes of turnover rate were observed, and there were differences between various parts of the skeleton.

Whole-body and profile counting are useful in studying the retention and distribution of radiopharmaceuticals administered for scintigraphy. The information is valuable for radiation dosimetry calculations and can also give an insight into physiological behaviour. The techniques have been applied to studies of lung, liver, lymph and other scanning agents.

^{52}FE STUDIES OF BONE MARROW DEPRESSION AND REGENERATION FOLLOWING LARGE FIELD RADIOTHERAPY

By S. C. Lillicrap, Heather A. Steere, H. M. Clink and M. J. Peckham

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^{52}Fe is in routine use for bone marrow imaging at the Royal Marsden Hospital. A dual-headed whole-body scanner with digital output, situated in a low background area, is used to obtain the marrow scan.

One of the studies undertaken has been to examine quantitatively the extent of depression, followed by regeneration and redistribution of the bone marrow, after large field megavoltage irradiation of the lymph nodes (usually mantle or inverted Y field, treated to at least 3000 rad). The scans of 20 patients with lymphoma (usually Hodgkin's disease) irradiated up to seven years before scanning have been compared with those of 19 patients with normal bone marrow and the percentage of normal marrow uptake plotted as a function of time after irradiation. The results have been correlated with the haematological status of the patients at the time of scanning. The increased iron uptake in unirradiated sites and extension of erythropoietic marrow along the long bones has also been estimated. The significance of the findings in relation to the treatment of patients who have had previous large field irradiation was discussed.

THE MEASUREMENT OF THE RATE OF BLOOD LOSS USING IRON-59 AND WHOLE-BODY COUNTING

By G. M. Owen, W. H. Thomson, J. A. F. Napier and A. Jacobs

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The whole-body counter used is based on four 150 mm diameter × 100 mm thick NaI(Tl) crystals which are mounted radially on a moving circular gantry in a steel room. The patient lies on the axis of the gantry which moves along his length. From experiments using a point source of ^{59}Fe in a Bush phantom, the optimum Compton energy band and end stop correction were selected to produce a sensitivity independent of the distribution of the radionuclide.

Following the intravenous injection of 1 μCi of ^{59}Fe, measurements in the whole-body counter were made, sometimes for several months, on the patient and also a reference source. The corrected counting rates were fitted by computer to a single exponential function and the gradient, expressed as % per day, used as an index of blood loss. This implies a single pool of iron, but since the patients were iron deficient and therefore had high utilizations, this is an acceptable assumption. Mean values of 0.03% per day were obtained in a group of normal males and also a group of postmenopausal females. A group of menstruating females had a mean value of 0.06% per day. Published data on blood loss were reviewed.

Examples were shown of the use of the technique in assisting in the diagnosis of some puzzling cases of iron deficient anaemia due to suspect menorrhagia or gastrointestinal bleeding. In clinical practice the pattern of the loss of ^{59}Fe as well as the overall rate of loss provided useful information.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

B.I.R. Library

The opening of the Institute's house for members to use the Library on Saturday mornings has been discontinued through lack of support. However, arrangements would be made for the Library to be opened between 10.00 a.m. and 1.00 p.m. on a Saturday if prior notice was given. Telephone 01–935 6237 or write to The General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Experimental and Clinical Applications of Krypton 81m

An all-day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology to be held at the Hammersmith Hospital, London, W12 on June 3, 1977. Registration and details from the General Secretary.

Progress in Experimental Radiotherapy

A meeting organized by the Netherlands Radiobiological Society in collaboration with the B.I.R. will be held on June 6–7, 1977 in Essex.

Subjects will include neutron radiobiology and radiotherapy, hypoxic cell sensitizers, chemotherapy and combined modalities.

Further details can be obtained from J. J. Broerse, Radiobiological Institute TNO, Lange Kleiweg 151 Rijswijk, The Netherlands, or S. B. Field, MRC Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12 0HS.

Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

Sixth International Conference on the Use of Computers in Radiation Therapy

Will be held at Gottingen on September 18–23, 1977. Further information from: R. E. Bentley, Physics Department, Royal Marsden Hospital, Downs Road, Sutton, Surrey, or Professor U. Rosenow, Strahlenabteilung, Unit.-Frauenklinik, D-34 Gottingen, Fed. Rep. Germany.

XIV International Congress of Radiology

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV International Congress of Radiology, Avenida Churchill 97—5th Floor, ZC 39, 20,000, Rio de Janeiro, Brazil.

Tumour Ultrasound '77

An international symposium on the science and clinical practice of ultrasound diagnosis and localization of tumours will be held in London, on December 5–6, 1977. This has been arranged in conjunction with the Annual Scientific Meeting of the British Medical Ultrasonics Group which will be held on December 7–8, 1977 at the same venue. A commercial and scientific exhibition will be held throughout both meetings. It is intended that the meeting will give a systematic coverage of the field and that the published proceedings will provide an up to date view of the subject. For registration and abstract forms or further details write to Dr. Ralph McCready, Department of Nuclear Medicine and Ultrasound, Royal Marsden Hospital, Downs Royal Sutton, Surrey, U.K.

Book reviews

"S", absorbed dose per unit cumulated activity for selected radionuclides and organs. By W.S. Snyder, M. R. Ford, G. G. Warner and S. B. Watson, pp. 257, 1975 (Published by The Society of Nuclear Medicine Inc. and available from M.I.R.D. Committee, 404 Church Avenue, Suite 15, Maryville, Tennessee 37801, U.S.A.). N.M./M.I.R.D. Pamphlet No. 11 $7.95 or with loose leaf binder $10.20

This valuable publication can be regarded as a synthesis of much of the physical data which have appeared over the past nine years in earlier pamphlets prepared for the Medical Internal Radiation Dose Committee of The Society of Nuclear Medicine. For each of 117 "radionuclides" (including 20 metastatic states), the authors have computed the mean absorbed dose to 20 "target organs" from each of 20 "source organs" containing a uniform distribution of the radionuclide; they take as their basic model a modified version of the "Standard Man" used in Pamphlet No. 5 for calculations of absorbed fractions for photons. The "cumulated activity" of the title is the time integral of that activity in the appropriate "source organ".

In a ten-page introduction the authors explain carefully the assumptions made in their calculations and the limitations of the computation methods used. They give particular attention to the methods adopted in dealing with absorbed dose to the bone marrow and to problems that arise if one attempts to adjust the results presented for different sizes of organ. They set out three examples showing how the tables can be used in calculating the absorbed doses arising from (a) ^{99}Tc^{m} localized completely in the liver, (b) ^{123}I localized in the liver and then eliminated via the gastrointestinal tract and (c) from a ^{99}Tc^{m} labelled compound of which a certain fraction is localized in bone.

Small adjustments have been made in the masses of body organs used in their phantom to bring this closer to the Reference Man of ICRP. Report No. 23. In addition, the procedures adopted for estimating absorbed dose to constituents of the skeleton have been refined. Thus a distribution of active marrow in the skeleton has been assumed which is based on data of R. E. Ellis, and for electron emitters deposited in bone, F. W. Spiers' methods have been used. All except six of the radionuclides in the "companion" volume, Pamphlet No. 10, are included (all at the highest values of atomic number) and ^{201}Tl has been added.

The tables should save considerable labour in computation of dose, in particular as one no longer has to refer to two or three pamphlets in this Committee series in order to find out the decay scheme for the radionuclide and appropriate values for the absorbed fractions for each energy of γ or X-ray.

Full use of these tables can, of course, only be made when data are available on the time-variation of activity of a particular radionuclide in each organ considered. A potential disadvantage of using these tables is that one can lose the "feel" of a problem and so become liable to error. However, many workers will appreciate that some of the essential work has been done for them and that direct reference to the data on decay schemes appearing in Pamphlet No. 10 and its predecessors will not be necessary.

This is a useful, well-produced publication, with discussions and data clearly presented, and is warmly recommended to anyone concerned with problems in the dosimetry of radiopharmaceuticals.

N. G. Trott.

Radionuclide decay scheme and nuclear parameters for use in radiation-dose estimation. By L.T. Dillman and F. C. Von der Lage, pp. 119, 1975. (Published by The Society of Nuclear Medicine Inc. and available from M.I.R.D. Committee, 404 Church Avenue, Suite 15, Maryville, Tennessee 37801, U.S.A). N.M./M.I.R.D. Pamphlet No. 10 $6.50 or with loose leaf binder $8.75

This volume in the well-known series of pamphlets prepared for the Medical Internal Radiation Dose Committee of the United States Society of Nuclear Medicine replaces two earlier pamphlets, Nos. 4 and 6 by L. T. Dillman, published in 1969 and 1970. In contains data for 122 radionuclides of interest in nuclear medicine. In this volume the decay schemes and the accompanying tables of input and output data are directly reproduced from the computer print-outs.

The opening section includes, with some minor editing, all the explanatory material given in the earlier pamphlet No. 4. The introduction to this section has been considerably extended; the authors explain in detail how data were selected and discuss the accuracy of the values presented, including the significance to be ascribed to figures given in the four decimal places presented in the tables: they explain that "trailing zeros do not usually represent significant digits in input data", and point out that experimental measurements of intensity of the various radiations "are rarely more accurate than 1–2% and often have errors of 10% or more".

The authors mention that, in reviewing data for the 54 radionuclides originally covered, major revisions were needed for 19 and minor for another 19; unfortunately these radionuclides are not identified.

The additional radionuclides now covered include ^{40}K, ^{47}Ca, ^{64}Cu and ^{90}Y among those long used in nuclear medicine, some introduced more recently such as ^{81}Kr^{m} and ^{111}In, and several that are unexpected, including ^{220}Rn and ^{230}Ra. ^{201}Tl does not appear.

As in the earlier pamphlets, the tables of data for individual radionuclides do require the user to be alert, since the sequence adopted (presumably as a necessary consequence of the computer procedure) groups together all radiation associated with particular transitions; in consequence concentration and good eyesight are needed in separating data for the charged particles which will, for most purposes, be treated as "non-penetrating" with absorbed fraction unity, and the data for electromagnetic radiation which will normally be "penetrating" with absorbed fraction less than one.

It is interesting to compare this compilation with its celebrated forerunner *Radiations from Radioactive Atoms in Frequent Use* of L. Slack and K. Way (1959). Slack and Way dealt with 18 radionuclides and they did, incidentally, list separately data for charged particles and electromagnetic radiation. Output data for ^{131}I in Slack and Way covered 19 charged particles and photons while 37 appear in Dillman and Von der Lage. It is perhaps some measure both of current productivity and anticipated sales that the present volume, dealing in much greater detail with 122 radionuclides, costs only 12 times as much as its excellent if slimmer predecessor. The loose-leaf form with the strong well designed binder should prove convenient in entering future amendments or additions.

The authors and their collaborators are to be congratulated on carrying through this extensive analysis which will surely be indispensable to anyone wishing to undertake dose estimations for any of the radionuclides listed.

N. G. Trott

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TEACHING BOOKLETS

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The Physical Aspects of Radioisotopic Organ Imaging, by K. G. Leach (1976) £1·50

No. 2
Introduction to the Principles of Diagnostic Ultrasound, by H. B. Meire and P. Armstrong (1976) £1·40

No. 3
Fundamental Aspects of Medical Thermography, by W. M. Park and B. L. Reece (1976) £3·40

Available from the Publications Office,
British Institute of Radiology,
32 Welbeck Street, London W1M 7PG

ERRATA

Owing to an Agency error, the telephone number of Actina X-ray division (Sakura X-ray film), page xxi is incorrectly shown.

The correct number should be

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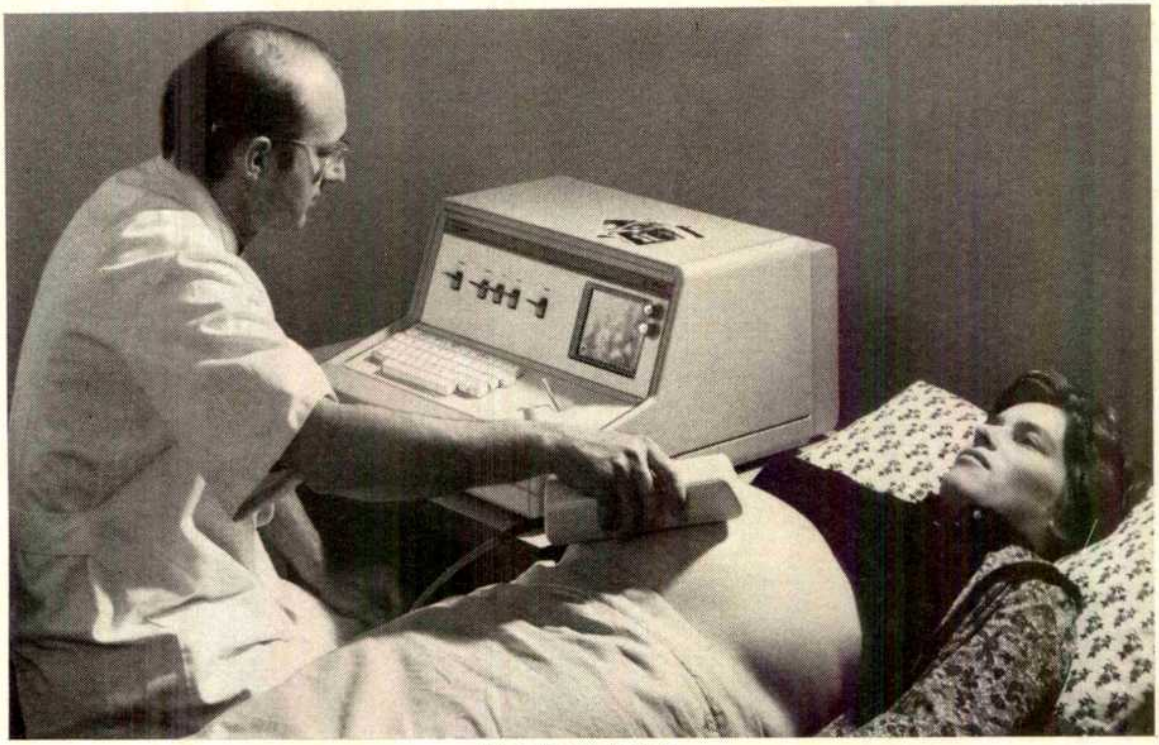

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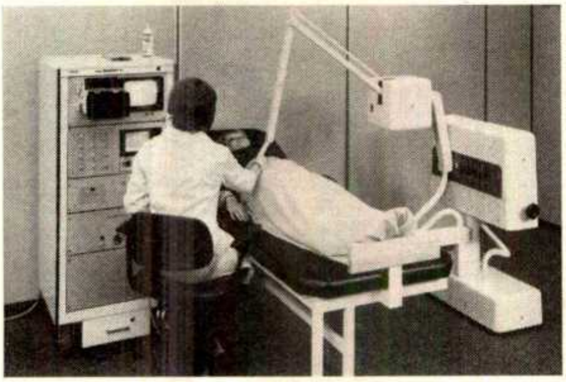

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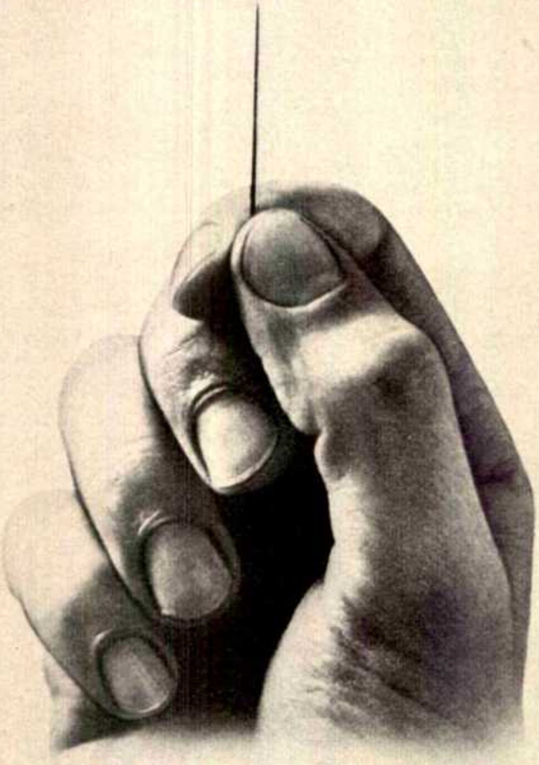

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Announcement

SOCIETY OF COMPUTED BODY TOMOGRAPHY

The Society of Computed Body Tomography, organized in January 1977, is composed of diagnostic radiologists active in the clinical utilization of this new imaging technique. Officers include Ralph J. Alfidi, M.D., President and Stuart S. Sagel, M.D., Secretary-Treasurer. The Society's purpose is to serve as a focal gathering point for the intimate exchange of scientific information between the experienced leaders in this field.

A Refresher Course on CBT sponsored by the Society and designed to convey current knowledge to the entire radiologic community will be held at the Islandia Hyatt House in San Diego, California, January 30 to February 2, 1978, with attendance limited to 250 registrants.

Further information about the Refresher Course may be obtained from Patrick F. Sheedy, 11, M.D., Scientific Program Chairman, c/o Department of Radiology, Mayo Clinic, Rochester, MN 55901. Additional faculty will include Drs. John Haaga, George Harell, Robert Hattery, Elias Kazam, Melvin Korobkin, Robert Stanley, David Stephens and Jack Wittenberg.

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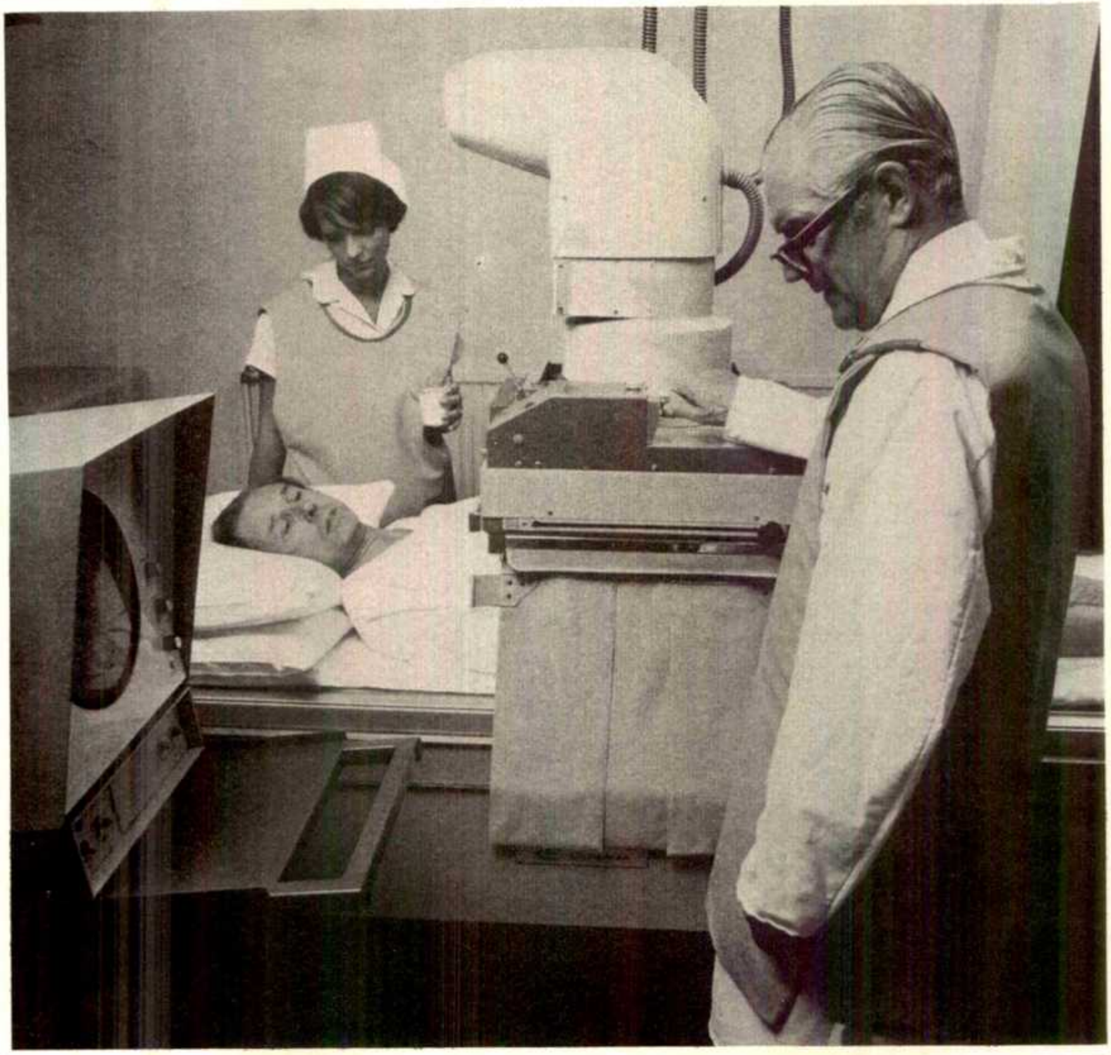

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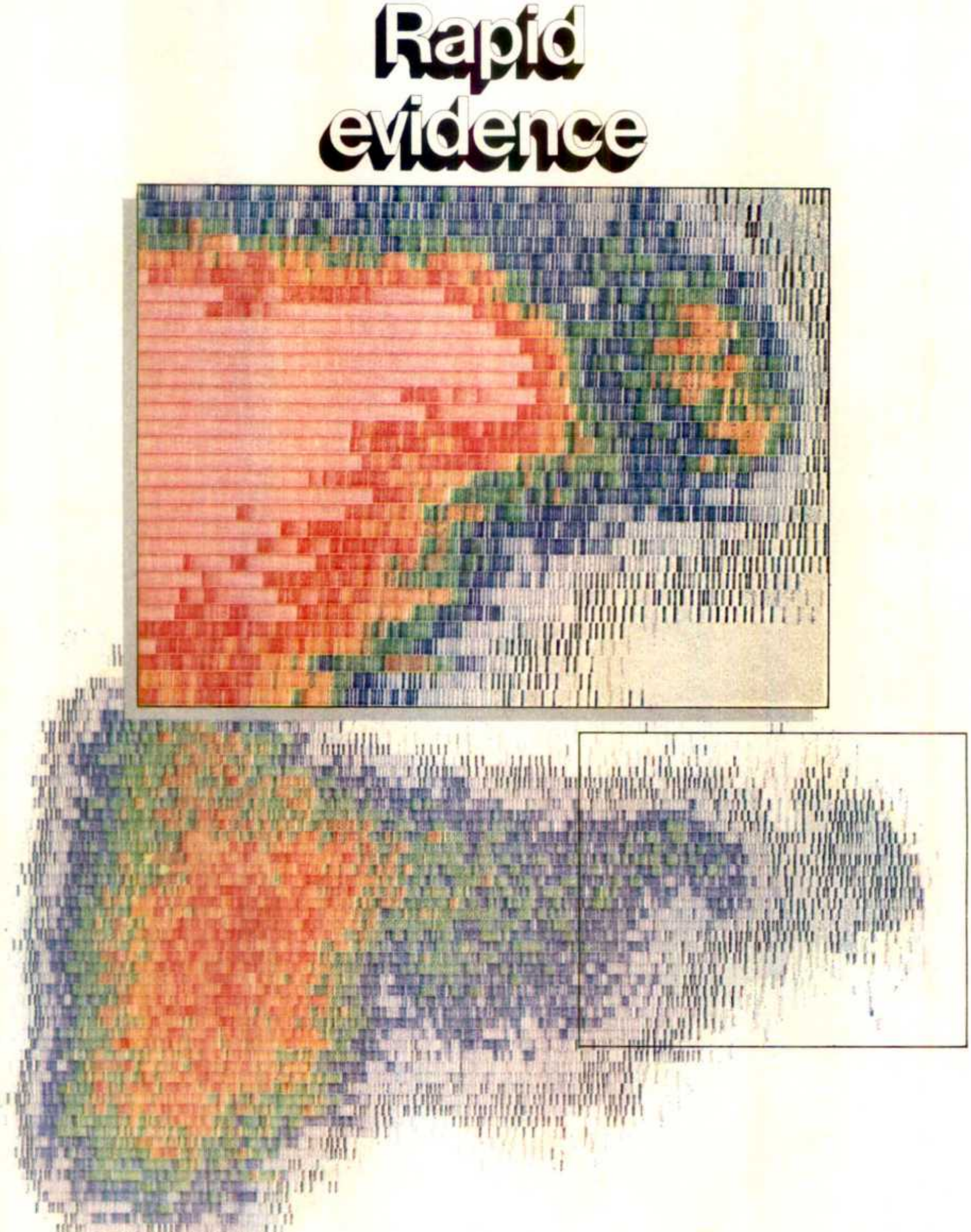

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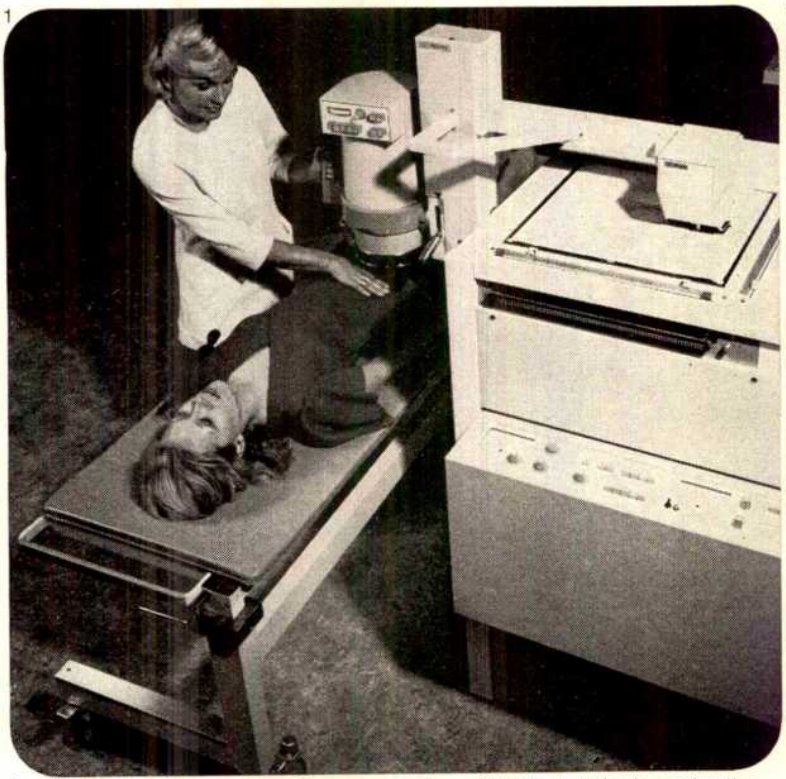

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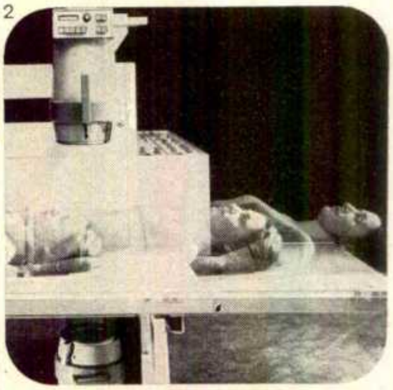

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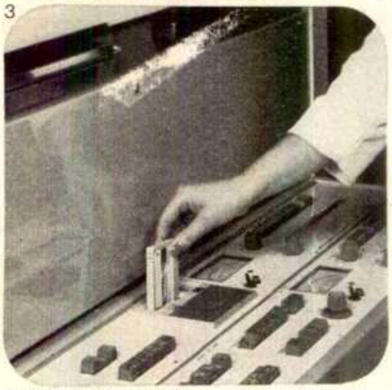

1 **The basic unit** comprises a 5in. over-table detector with motor-driven vertical adjustment of the detector head allowing virtually any patient table or hospital bed to be used.
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2 **Total body and profile scanning** can also be performed by means of an optional motor-driven tabletop. This enables two-speed longitudinal movement of 100mm/min (approx. 4in./min) and 200mm/min (approx. 8in./min) and facilitates profile scanning using slit collimators. With the total body version the scanning area is 400 x 1600mm (15¾in. x 63in.); scintigram reduction factor being 4 : 1.
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3 **A second colour printer and photo scan unit** considerably extends the versatility of the Philips Universal Scintillation Scanner by enabling other original scans, based on different parameters, to be obtained. Furthermore, recording and storage of original scanning data can be achieved by means of a four track compact-cassette recorder. In the playback mode recordings can be reproduced using different scanner settings, i.e. different colour printer control signals.

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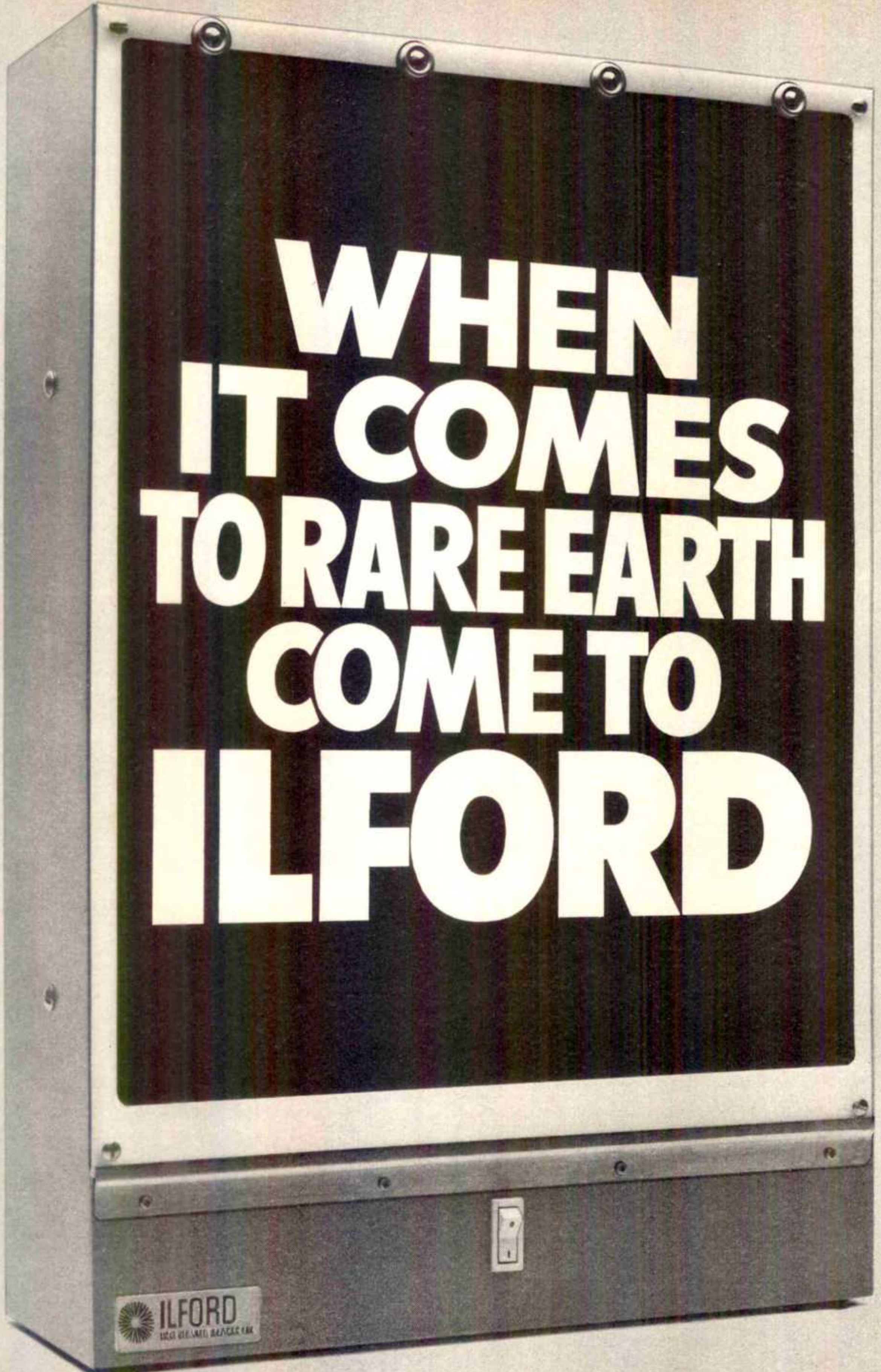
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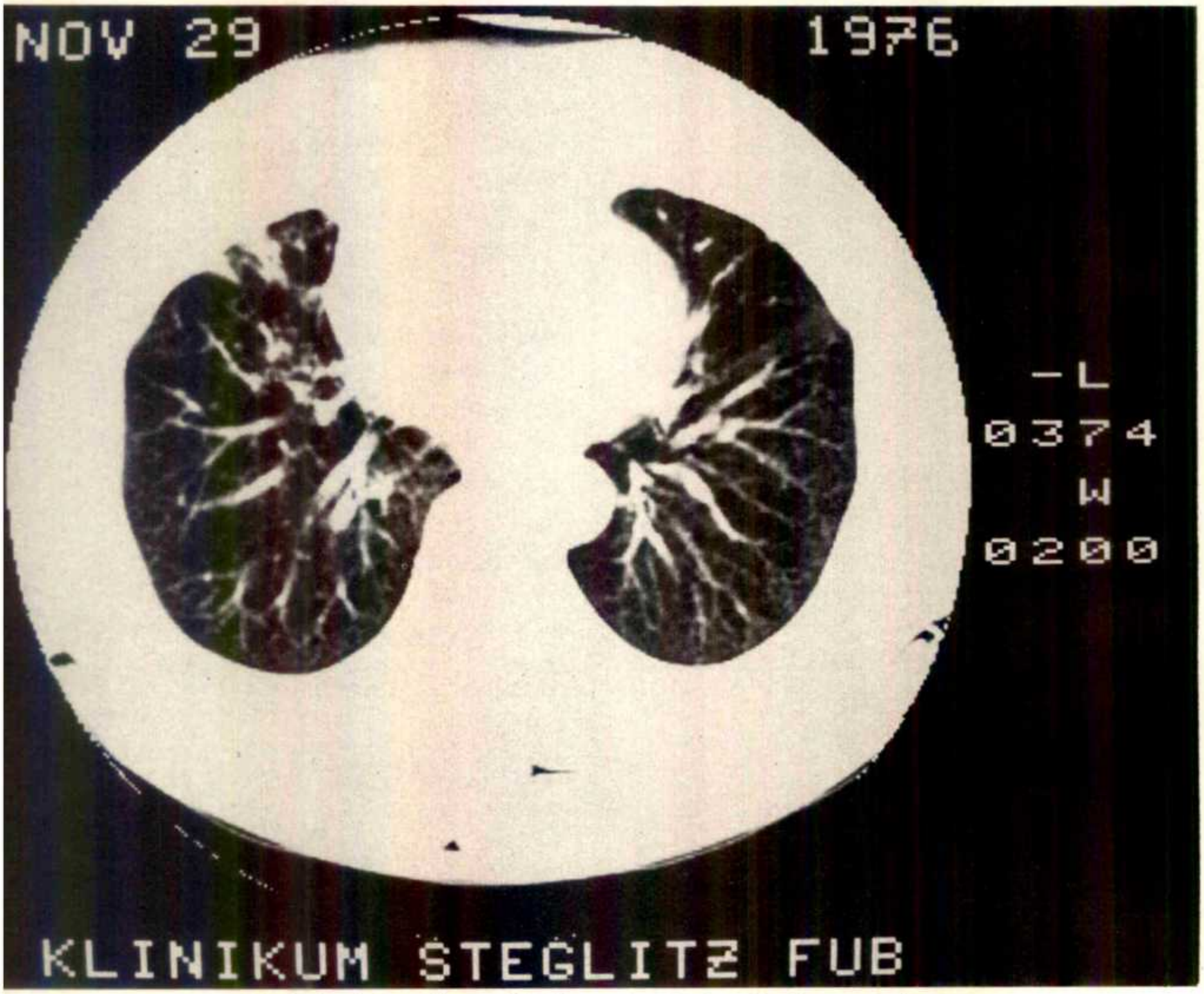

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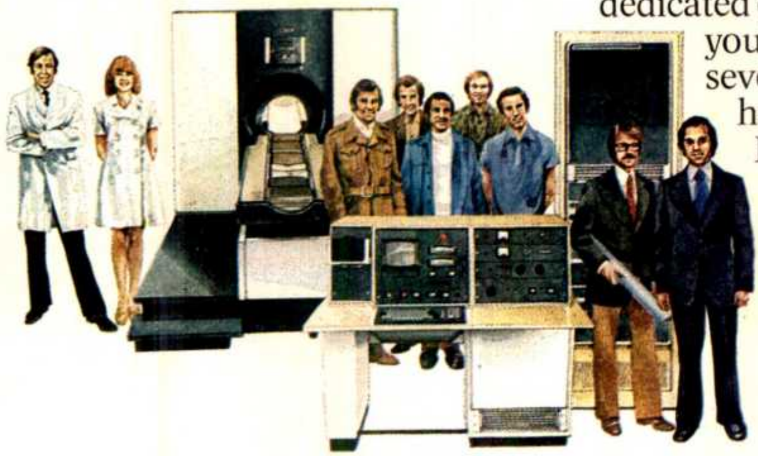

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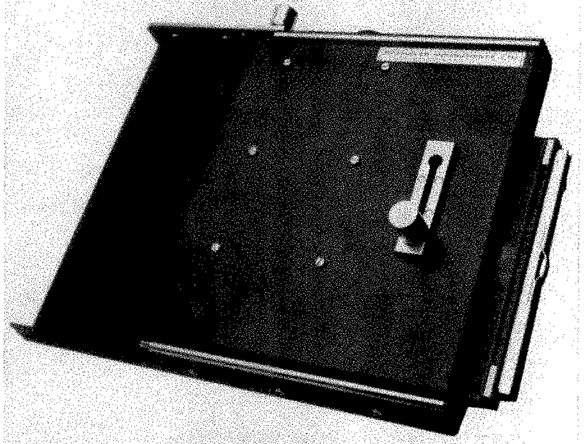

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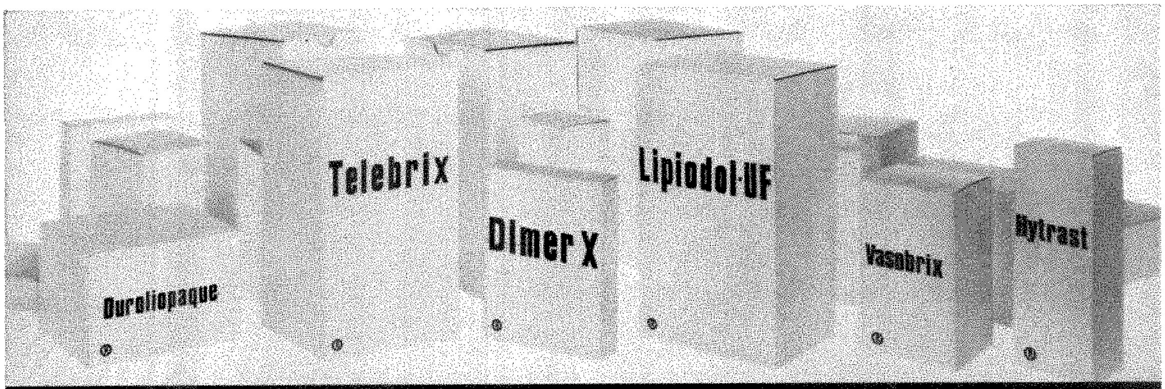

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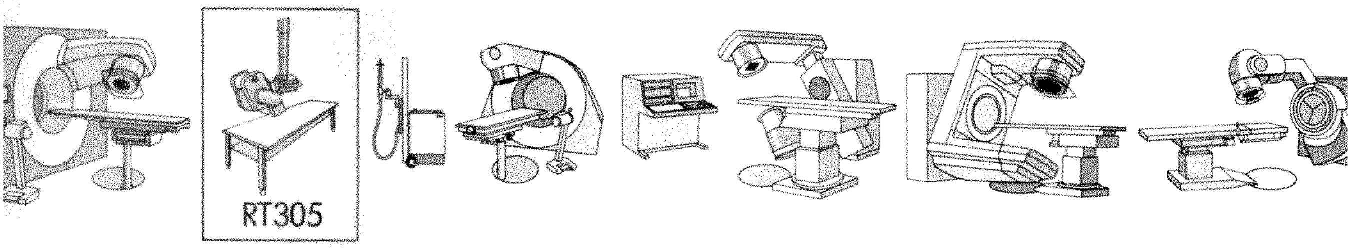

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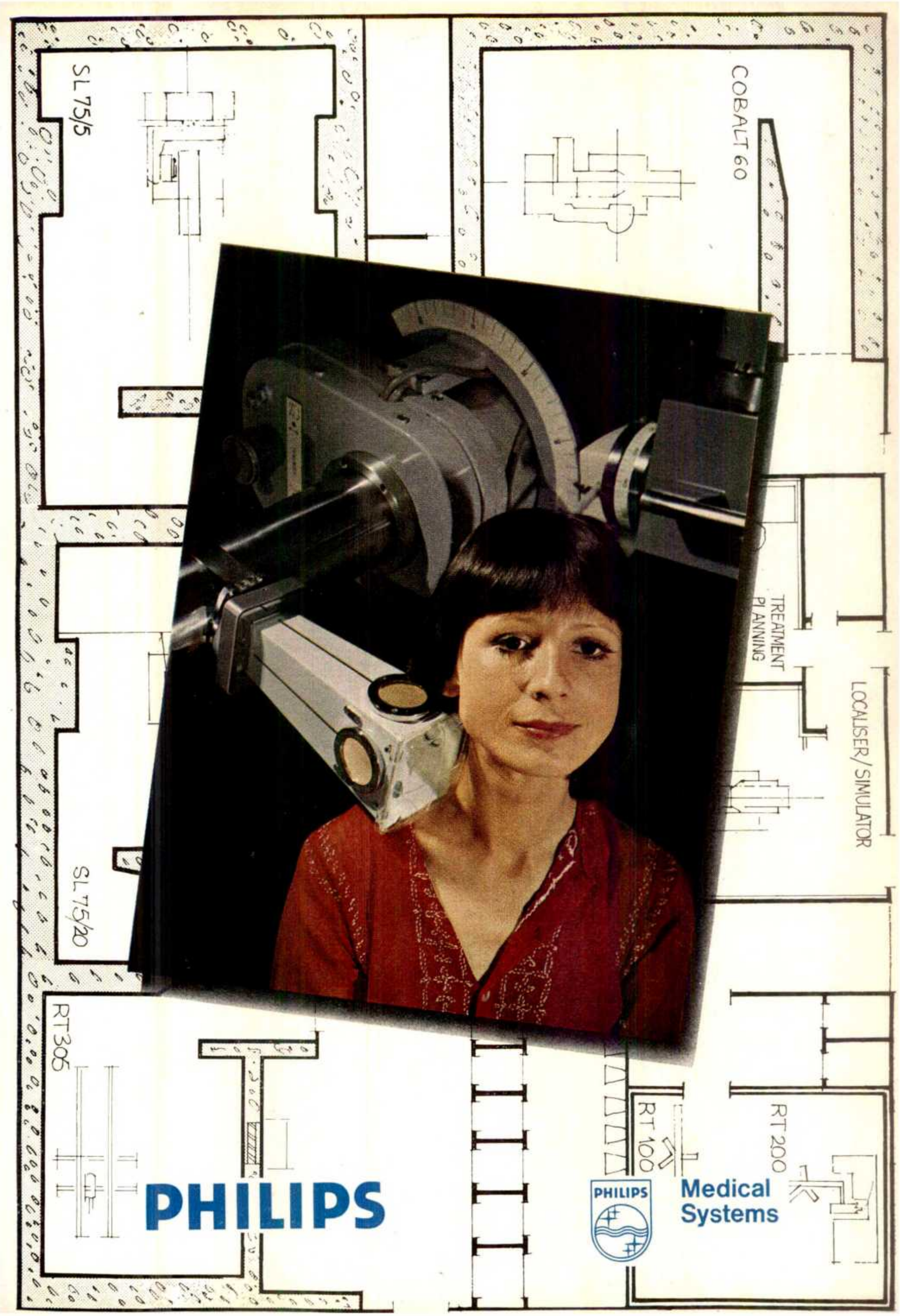
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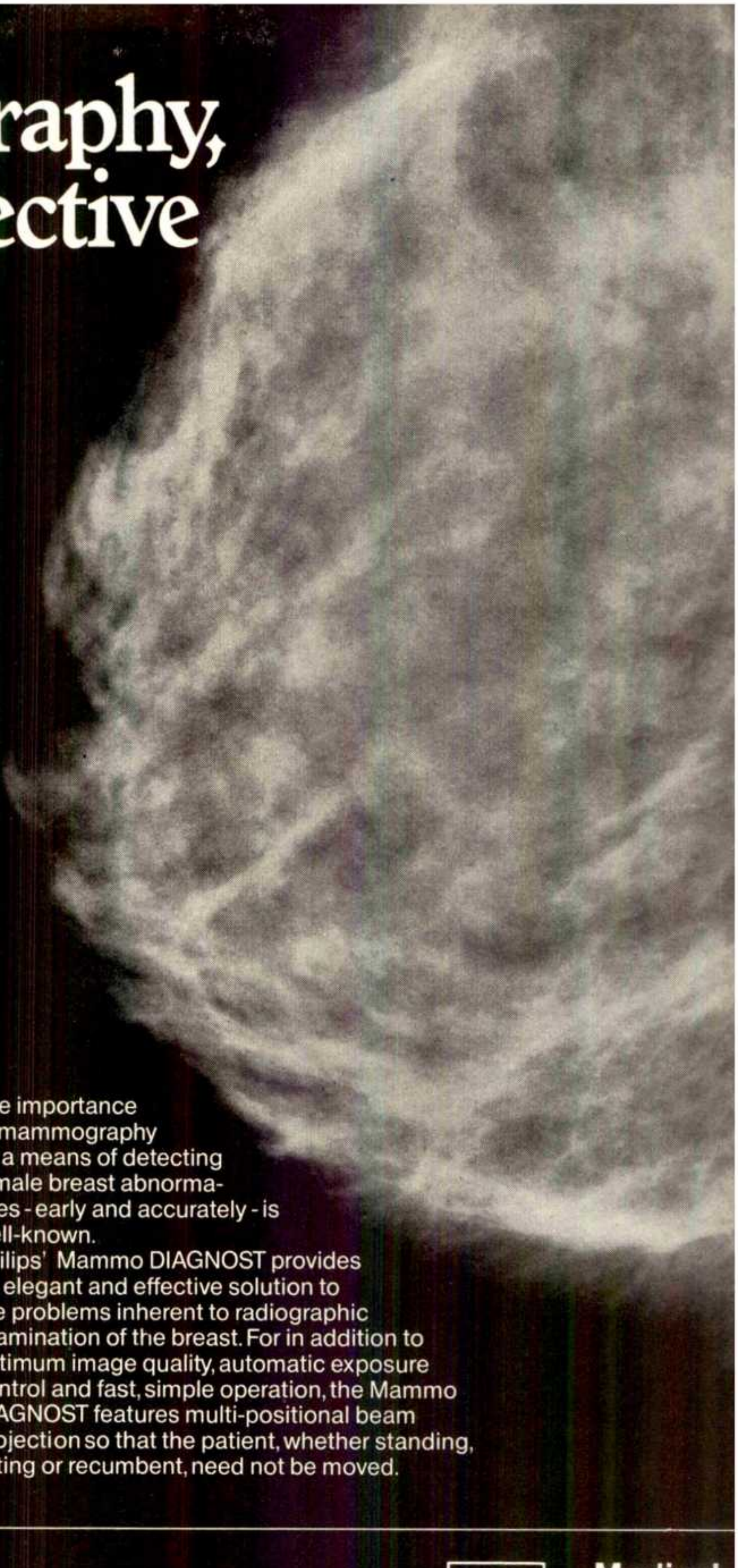

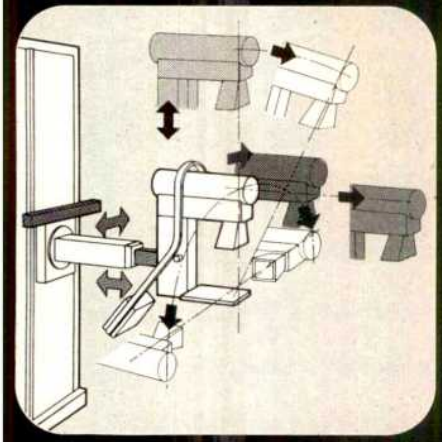

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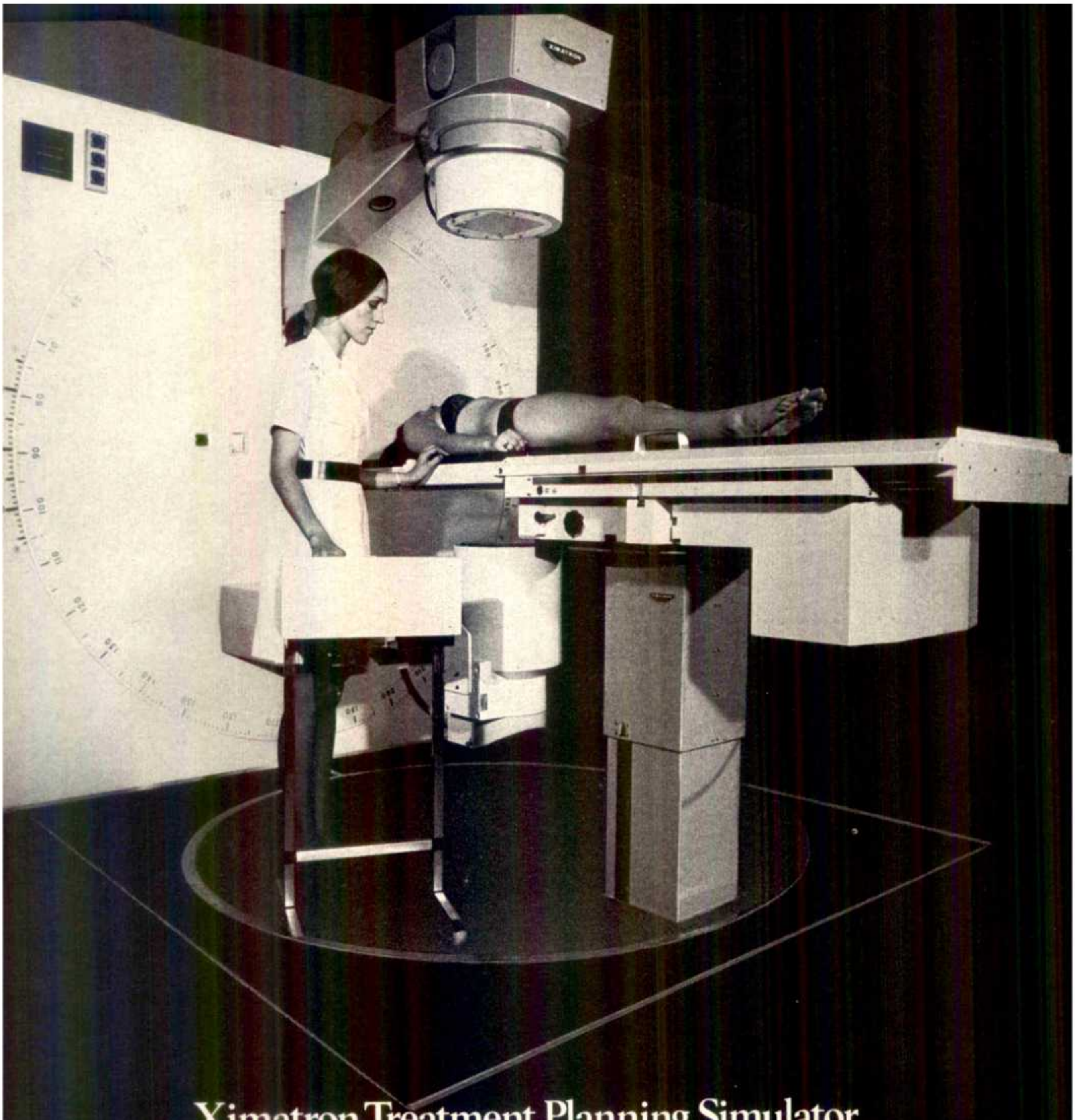

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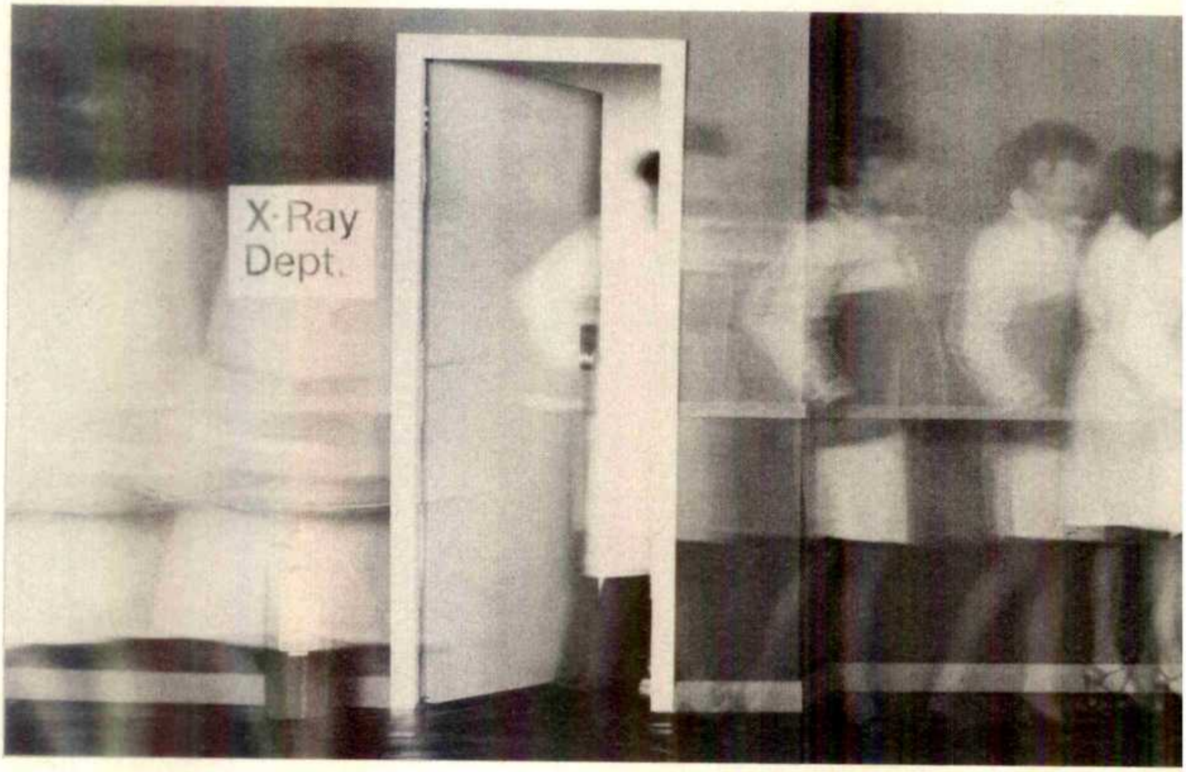

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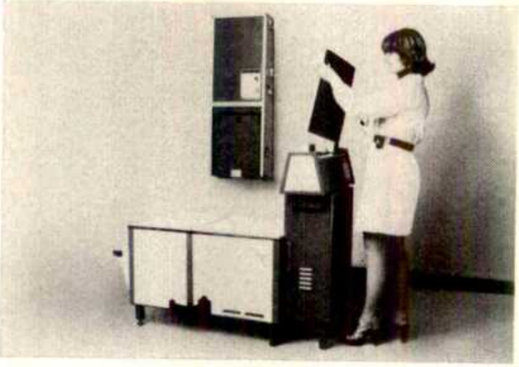

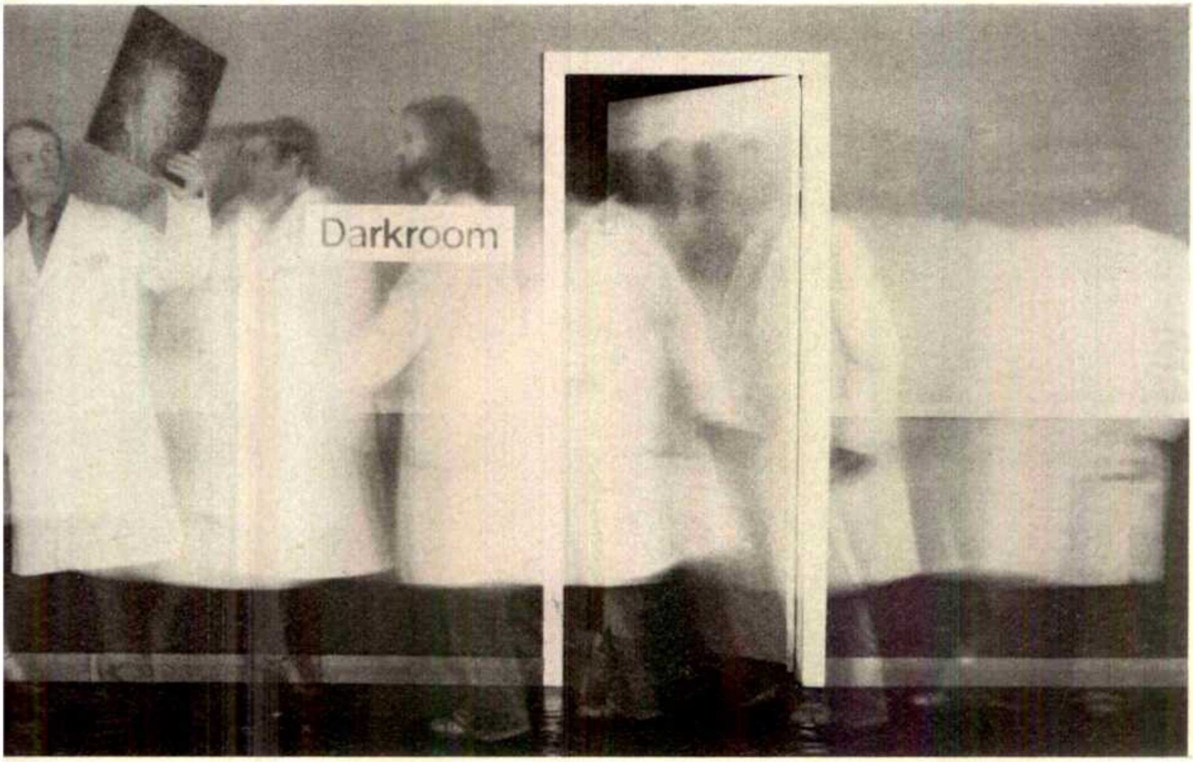

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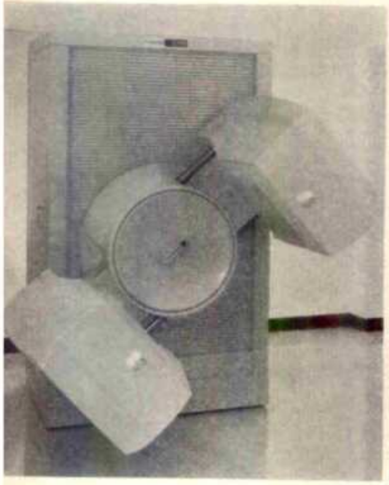

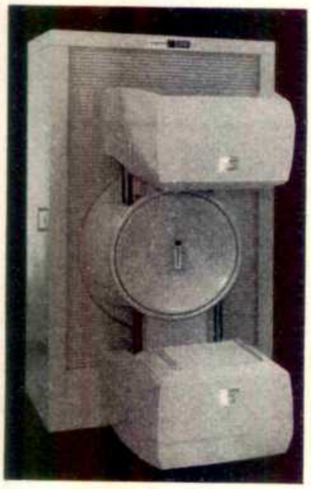

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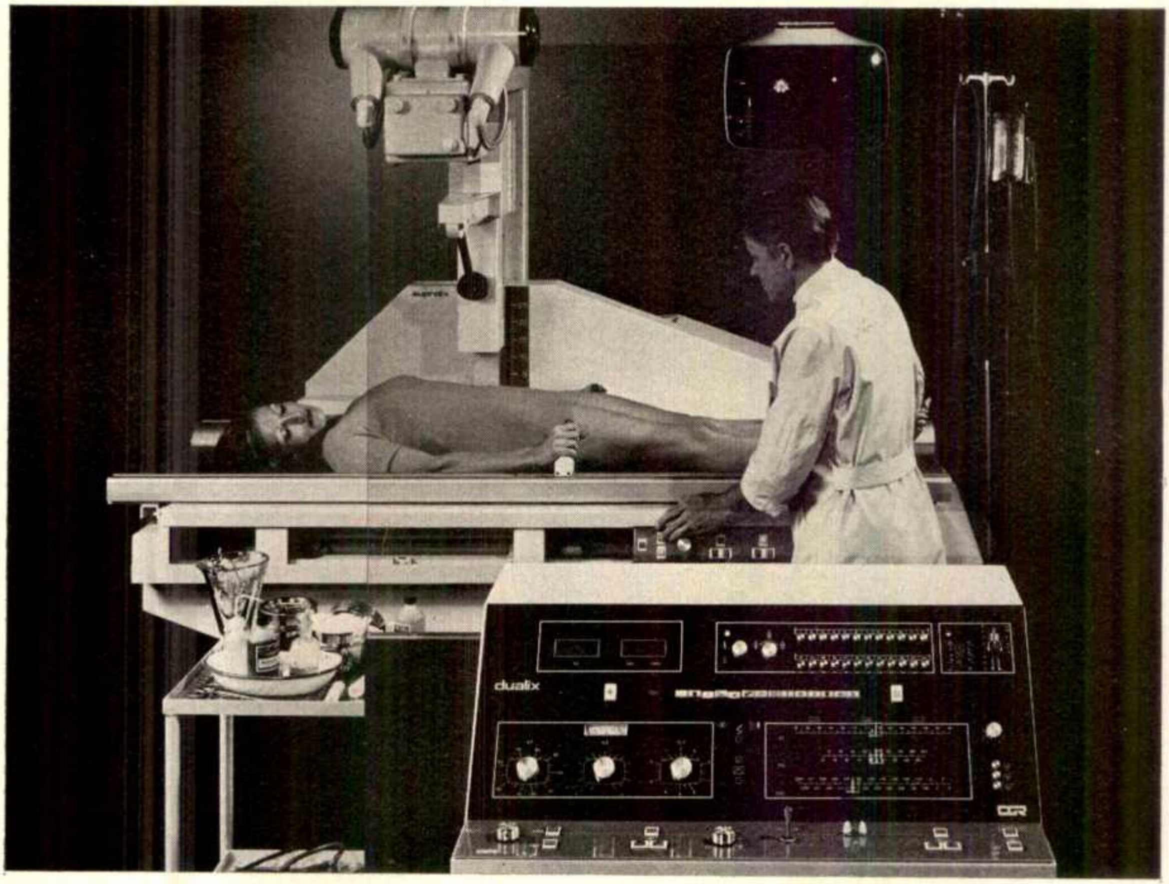

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EDITED BY D. N. EDWARDS, M.B., F.R.C.R.

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Data Processing in Radiobiology	A. Wambersie, C. A. Joslin
Treatment Planning: The Input of Data	C. A. Joslin, E. Sternick
Treatment Planning: Methods of Dose Computation	R. E. Bentley, J. C. Rosenwald
Treatment Monitoring and Documentation	H. Dahlin, A. Glicksman
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VOLUME 50 NUMBER 595 JULY 1977

The British Journal of Radiology

Hypothesis

Elkind recovery and "sub-lethal damage": a misleading association?

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(*Received November, 1976 and in revised form February, 1977*)

ABSTRACT

While some failures in radiation sterilization of tumours may be attributable to the existence of foci of hypoxic cells, another possibility is that Elkind recovery, during the fractionation intervals in a conventional radiotherapy régime, may confer more sparing on tumour cells than on the clonogenic cells in the normal tissues at risk. It is therefore of clinical as well as of fundamental interest that more should be learned about the cellular events during the period of Elkind recovery.

That phenomenon is intimately bound up with the occurrence of "shoulders" in many survival curves for eukaryotic cells. It is commonly accepted that these result from the cells' requirement for an accumulation of damaging events before they lose proliferative capacity: two or more "hits" for the inactivation of each target, or the inactivation of two or more targets, the survival of any one of which would suffice to leave the cell viable. In that context, complete Elkind recovery represents the repair of every "sub-lethal lesion" in all surviving cells.

Comparatively little attention has been paid to a fundamentally different view of survival curve shoulders, according to which they represent a dose range within which some *potentially* lethal lesions are repaired; but the cells' repair capacity decreases with increasing dose, until the survival curve approaches a final slope determined by the number of unrepaired lesions inflicted per unit dose. However, surviving cells will recover their repair capacity, during a radiation-free interval, and that is how Elkind recovery would be defined.

Many experimental observations are well accommodated by that latter "repair" model. Sinclair (1972) suggested that repair might be mediated by a specific factor, "Q" factor, and the hypothesis would gain plausibility if Q-factor could leave the nucleus and even cross the plasma membrane. However, the phenomenon known as "repair of potentially lethal damage" imposes the requirement that there is also another class of lesion the repair of which is independent of dose.

The design of experiments aimed at elucidating the phenomenon of Elkind recovery must, to a large extent, depend on the basic assumptions made to account for survival curve shoulders. Since the phenomenon is central to the mechanism by which radiation kills cells, and also has clinical implications, it would seem important that one or other of these mutually exclusive explanations should be validated.

In those tumours which fail to be controlled by radiotherapy there may be assumed to be cells on which the cytocidal action of radiation is not sufficiently effective. In its role as a supportive discipline, radiobiology has as important aims the discovery of reasons for this insufficiency, and of methods for dealing with it. Laboratory observations on the protective effect of hypoxia led to the suggestion that the presence of a small fraction of hypoxic cells in human tumours might be one reason for failure in local control. Some proposals for ways of overcoming this problem have been put into effect as clinical trials, and the topic continues to be a theme of ongoing research.

There are few radiobiological phenomena of as wide a generality as the "oxygen effect". There is one, however, which may be at least as important clinically as protection by hypoxia, namely that known generally as "recovery from (or repair of) sublethal damage". Because of the pioneering work of Elkind and his colleagues on this phenomenon, it is sometimes referred to as "Elkind repair" or "recovery", and I shall use that term, not only for brevity, but also because the phrase "sub-lethal damage" may have been responsible for setting up a wrong conceptual framework for our approach to understanding the mechanism.

The majority of cell survival curves for eukaryotic cells are of the type known as "shouldered": that is, there is a dose range, starting at zero dose, within which the sensitivity of the cells is less than at higher doses. It is usually stated that the lesser sensitivity is attributable to the cells' capacity for accepting lesions that are "sub-lethal"; when sufficient sub-lethal lesions have accumulated within a cell, a final event will destroy its proliferative capacity. On the assumption that this represents the reason for the existence of the "shoulder", it is the general experience that cells containing only sub-lethal lesions are capable also of repairing all of them, given sufficient radiation-free time and the appropriate conditions.

Thus the survivors of a first dose fraction will, after full recovery, respond to subsequent irradiation as if they had not previously been exposed. If the dose-rate is low enough there may be sufficient time for repair during the exposure, so the sparing effects of fractionation and low dose-rates are well accounted for by the experimental observations on Elkind recovery. If that form of recovery occurred to a greater extent in the stem cells of normal tissues than in clonogenic tumour cells, the fractionation schedules commonly used in radiotherapy would always result in therapeutic gain. The extent of Elkind recovery in any cell line may be quantified, roughly, by the parameter D_Q, or quasi-threshold dose. This is, in effect, the additional dose required per fractionation interval to achieve the same effect as if the total dose were given without fractionation. If D_Q is greater for normal than for tumour cells, fractionation must be advantageous. But the converse may sometimes obtain.

Various techniques have been used to measure, or estimate, the parameter D_Q for stem cells in some normal tissues, but only indirect methods are available for estimating its magnitude for tumour cells *in vivo*; tissue culture experiments on tumour cell lines cannot be relied upon to give the relevant answers (Alper, 1974a). Some observations on animal tumours suggest that D_Q for the clonogenic cells is just as variable from one line to another as it is for cells in normal tissues or, for that matter, for cells grown in culture (Withers, 1970; Alper, 1972; Howlett *et al.*, 1975). If this variability exists in human tumour cell lines, there may well be some for which D_Q is greater than for the normal cells at risk, in which case an ordinary fractionation régime, while sparing the normal tissues, would spare the tumour even more.

Some consideration has been given to the possibility of developing methods that would specifically reduce D_Q in tumour cells. Densely ionizing radiation (of high Linear Energy Transfer, or LET) is well known to reduce the magnitude of the shoulders of cell survival curves but, as yet, there are no means of predicting how great the reduction will be for any given cell line if, say, neutrons are used for irradiation instead of low LET radiation. If the reduction is greater for the tumour than for the normal cells, this will provide an additional reason for a therapeutic gain from the use of neutron therapy (Alper, 1972). But the converse might be true, in which case neutrons would be less effective than photons (Howlett *et al.*, 1975). Another possible approach has been suggested, arising from the observation (in tissue culture experiments) of the great variability in D_Q as synchronized cells proceed from one mitosis to the next (Fig. 1). If this variability occurs also *in vivo*, and if tumour cells could be irradiated during cycle stages within which D_Q is small, there might be an important therapeutic gain. But no method for selective synchronization of tumour cells has been mooted.

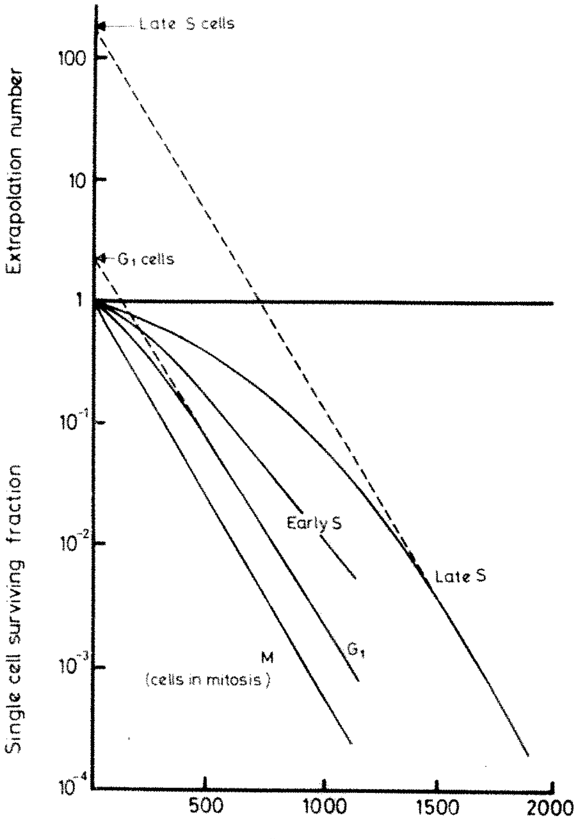

Fig. 1.

Survival of V79 Chinese hamster cells, synchronized and irradiated in different stages of the cell cycle. Adapted from Sinclair and Morton (1966).

Inconsistent Interpretations of Survival Curve Shoulders

Methods for solving the problem of Elkind recovery in tumour cells might emerge from a clearer understanding of the mechanism. Some experimental work of Elkind *et al.* (1967) did suggest to them that the postulated "sub-lethal lesions" were not qualitatively different from lethal ones. But many procedures or agents modify cell survival curves by changing the "shoulder width" alone, with no concomitant change in the final sensitivity to lethal events. This would represent a change in that property of the cell which determines whether a damaging event shall be lethal, or "sub-lethal", *i.e.* cumulative, if Elkind recovery is identified with repair of sub-lethal damage.

While that identity is widely assumed in the interpretation of dose-rate and fractionation effects, a different (and inconsistent) view is sometimes expressed, namely that the shoulder itself is indicative of repair—in the sense that repair of *potentially* lethal lesions occurs in the dose range covered by the shoulder of a survival curve. For example, Sinclair's work (1972, 1973) on modification of changes in radiation response, as cells in culture proceed through their cycle, led him to conclude that there is some factor, which he called *Q*, varying through the cycle, which either "protects the cell from damage, or *repairs radiation damage before it can be expressed*" (Sinclair, 1973, my italics). But, by definition, sub-lethal damage never is expressed, at least when survival or non-survival is the test; and, if the *Q* factor were responsible for the sort of changes illustrated in Fig. 1, as the cell proceeds through its cycle, it could "protect" only by converting otherwise lethal hits into sub-lethal ones, if "capacity for accumulating sub-lethal injury" is indeed what the shoulder width represents. Sinclair's statement, and his results, imply rather that *Q*-factor is associated with lesions which are potentially lethal, that is, are capable of causing the cell to die even if it suffers no further hits.

It is worth examining the historical basis for the conceptual association of survival curve shoulders with accumulation of "sub-lethal lesions". That phrase could, of course, be applied to any effect of radiation that failed to kill the cell (in this context, to destroy its proliferative capacity), but it has come to acquire a restricted meaning in radiobiology and radiotherapy, in the sense that it defines the damage dealt with when Elkind recovery occurs. The first use I have encountered of the word "sub-lethal", in that sense, is in a paper by Atwood and Norman (1949). This was, basically, a discussion of the mechanism by which conidia of Neurospora were killed by ultraviolet light: was the shouldered survival curve better described as "Multihit" or "Multi-target" in nature? The multihit curve is derived from the assumption that cell death is a consequence of inactivating a target (or more than one) that would survive n-1 hits, but succumb to the nth one; whereas a multi-target curve would result if the cell contained n targets, and remained viable as long as any one of them escaped a hit. The first survival curve constructed for mammalian cells was shouldered, with extrapolation number two (Puck and Marcus, 1956) and was interpreted as showing two-target, single-hit action. Later workers, while observing higher extrapolation numbers for other cell lines, tended in the main to accept the multi-target model, according to which an n-target cell would survive as long as it had experienced hits in only n-1 targets. It is in that sense that the phrase "sub-lethal injury" is used, in association with the phenomenon of Elkind recovery. Although the association has been widely accepted, there are difficulties in reconciling it with the concept of specific targets for cell killing, on any plausible assumption of what the target or targets might be in a mammalian cell. Why should the reparability of all sub-lesions be lost when, and only when, the last one has been inflicted? The multi-target model, in particular, demands that the cell remain capable of repairing n-1 out of n targets that have been hit, presumably at random, but is rendered incapable of doing so when the nth one has been damaged.

A sometimes preferred alternative to multi-target or multi-hit models for shouldered cell survival curves is that proposed by Kellerer and Rossi (1972a). They postulated that radiation of low LET achieves its effects mainly by the interaction of two sub-lesions engendered by separate electron tracks—the "dual radiation action" hypothesis. Dose-rate and fractionation effects are interpreted, on that hypothesis, as manifestations of a limited time within which the first sub-lesion remains able to interact with the second: in other words, identification of Elkind recovery with "repair of sub-lethal lesions" follows from the Kellerer and Rossi model for cell killing as well as from "multi-target" and "multi-hit" models—though the latter models embody the possibility of large numbers of hits or targets, not just two.

In summary, the most generally accepted conceptual framework for an explanation of Elkind recovery is that shouldered survival curves with low LET radiation result from the requirement for two or more sub-lethal lesions to the cell if it is to be killed; the restoration of the "shoulder" to the survival curve for cells that have acquired all sub-lethal lesions but the last, fatal one, is envisaged within that framework. Have these concepts constrained our thinking, and therefore our methods of experimental attack? Much less account seems to have been taken of models for shouldered cell survival curves that do not postulate an accumulation of sub-lethal lesions before the cell is killed.

REPAIR MODELS

These have in common the concept that repair of some *potentially* lethal lesions occurs concurrently with their induction, or in the period before the cell goes into division; and that the capacity for repair is limited, either because the rate at which lesions are induced is greater than that at which they are repaired, or because the repair mechanism becomes "saturated", or is itself depleted by radiation. If the initial slope is not zero, and a "final" slope can be fitted to an experimentally derived survival curve, a reasonably good description can be obtained by various dose functions containing three parameters: the basic requirement is that the function equated to the logarithm of surviving fraction approximates to linear functions of dose both at low and at high doses. That requirement is, of course, the basis also for models that invoke "sub-lethal lesions", but are modified to allow for a non-zero initial slope: the "multi-target-plus-single-hit-component" model, for example, probably the one most frequently invoked. The Kellerer–Rossi model, which also belongs in the "sub-lethal lesion" group, allows for an initial negative slope at zero dose, but no defined final slope. Kellerer and Rossi (1972a) regarded their model as applicable mainly in the low dose region, and have suggested (Kellerer and Rossi, 1972b) that, in respect of RBE relationships, their model would lead to the same high-dose approximation as the multi-target single-hit model.

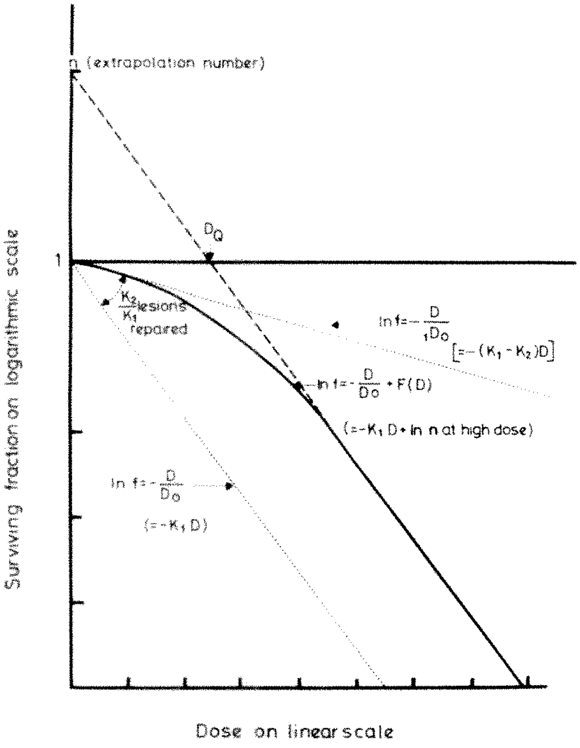
n (extrapolation number)
D_Q
1
$\frac{K_2}{K_1}$ lesions repaired
$\ln f = -\frac{D}{{}_1D_0}$
$[= -(K_1 - K_2)D]$
$\ln f = -\frac{D}{D_0} + F(D)$
$(= -K_1 D + \ln n$ at high dose$)$
$\ln f = -\frac{D}{D_0}$
$(= -K_1 D)$
Surviving fraction on logarithmic scale
Dose on linear scale

FIG. 2.

Diagrammatic representation of concept on which various "repair models" are based. $F(D)$ represents an unspecified function of dose that approximates to k_2D at zero dose and to $\ln n$ at high dose.

Some "repair models" have been proposed to account solely for shoulders on survival curves—particularly when those pertain to the action of ultraviolet light on bacteria (*e.g.* Ginsberg and Jagger, 1965; Haynes, 1966). But a model proposed by Powers (1962) to account also for Elkind recovery has been formally developed by Orr *et al.* (1966) and by Laurie *et al.* (1972). The basic idea of repair models is illustrated in simple form in Fig. 2. It is postulated that the cell survival curve would be represented by an exponential of slope $-D_0^{-1}$, if repair did not occur. If the cells were biochemically equipped to repair some of the potentially lethal lesions, the survival curve would again be exponential, but with lesser slope $-{}_1D_0^{-1}$, that is to say $({}_1D_0^{-1} - D_0)/{}_1D_0$ of the potentially lethal lesions would be repaired. But if the repair capacity of the cell were limited, the slope of the curve would increase, with increasing dose, and would finally approach $-D_0^{-1}$. Thus, with no repair of potentially lethal lesions, the survival curve could be written

$$\ln f = -\frac{D}{D_0} \text{ (or } -k_1D,\ k_1 \text{ being the inactivation constant)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

whereas, if all reparable lesions were repaired, however large the dose, it would be written

$$\ln f = -\frac{D}{{}_1D_0}, \text{ or } \ln f = -(k_1 - k_2)D \quad . \quad . \quad . \quad (2)$$

However, the repair capacity is assumed to decline as a function of dose (or of number of potentially lethal lesions inflicted), so the term $+k_2D$ in equation (2) must be replaced by some function which approximates to k_2D at low dose, and to $\ln n$ or $\frac{D_Q}{D_0}$, at high dose, just as the multi-target equation does.

Such models may generally be expressed, therefore, as

$$\ln f = -k_1D + F(D) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$F(D)$ represents a function of dose which has the required low and high dose approximations.

Various versions of such a function have been proposed, the authors basing their derivations on their chosen assumptions and evidence as to the mode of decline in repair capacity. For example, in the model of Ginsberg and Jagger (1965) and of Haynes (1966), both developed to account for shapes of survival curves of bacteria after UV irradiation, the repair term (*i.e.* the element $F(D)$ of equation (3)) is intended to represent an exponential decline in repair capacity. In both models, the extrapolation number is regarded as representing the total number of lesions per cell that can be repaired. This is determined either by time available for repair (Ginsberg and Jagger, 1965) or by the amount of a repair enzyme that can function before it is depleted by radiation action or by "saturation" of the repair system (Haynes, 1966).

The "pool" model of Laurie *et al.* (1972), so called from Powers' suggestion (1962), is not easily translated into the simple form represented by equation (3), although in essence the meaning is not different. They interpret the extrapolation number, n, as the number of units per cell of substance capable of repairing potentially lethal lesions before these are biochemically fixed. As with other repair models devised to account for shoulders to survival curves, the extrapolation number is dissociated from any concept of multiplicity of sub-lethal lesions that have to be accumulated before the cell is killed.

Thus there is a fundamental difference in the interpretation of Elkind recovery, depending on whether the mechanism of cell killing is conceived of in terms of a repair model, or of a multi-sub-lethal lesion model for a shouldered survival curve; the two concepts are mutually exclusive. According to the latter more familiar concept, the shouldered survival curve itself provides no evidence of repair; this can be observed only when survivors of a dose of radiation remain in appropriate conditions during a radiation-free interval, and are then subjected to further irradiation. Repair models, on the other hand, are based on the assumption that the shoulder itself is evidence both that repair of potentially lethal lesions occurs, presumably at some time before the cell goes into its first division after irradiation, and that repair capacity declines with increasing dose. Laurie *et al.* (1972) adopted Powers' suggestion (1962) that Elkind recovery is the replenishment of a "pool of intracellular constituents or states" that are required for repair.

Some treatments applied to cells before, during or after irradiation have been shown to change only, or mainly, the extrapolation numbers of survival curves and certain features of Elkind recovery are well established. Considered together, these observations suggest that the recovery phenomenon, as accounted for in repair models, must depend on a factor (or factors?) of greater specificity than is suggested by the word "pool". It is a simplification, in the first instance, to assume the existence of only a single factor. For brevity, I shall call this the Q-factor, following Sinclair (1972).

"REPAIR OF POTENTIALLY LETHAL DAMAGE"

It should be emphasized at this point that the potentially lethal lesions dealt with by the postulated Q-factor must be of a different category from those subject to what has become widely known as "repair of potentially lethal damage" (Phillips and Tolmach, 1966). That form of repair is associated with the observation of decreased terminal slopes of survival curves as, for example, occurs when cells of certain lines are held at low temperature for an interval after irradiation (Beer *et al.*, 1963; Whitmore *et al.*, 1970); or when irradiated cells can be left *in situ* and plating delayed, for example from tumours irradiated *in vivo*, or from monolayers of cells in stationary stage *in vitro* (Hahn and Little, 1972). Since "repair of potentially lethal damage" is commonly identified with a decrease in the sensitivity of the cells in the higher dose range, and is, indeed, thought in some cases to be dose-multiplying, the agent of repair is clearly not subject to depletion. To avoid confusion with those lesions which putatively require Q-factor for repair, it will be as well to designate the two classes by special terms—let us say P and Q lesions.

In a simple repair model, represented by equation (3), it is assumed that the basic mode for cell inactivation is a single-hit process—without repair, cell survival would be exponential. Single-hit inactivation of targets is, of course, the basis of the multi-target model: it is multiplicity of targets, not of hits, that is postulated. The concept that a cellular target may be inactivated by a single energy-deposition event conforms with the general experience that inactivation of sub-cellular model targets, like viruses, is always exponential: including inactivation of double-stranded DNA viruses. But any exponential may be the resultant of two or more exponential components, and it is plausible that living cells contain a multiplicity of targets; not as envisaged in multi-target models, which posit that the cell survives as long as any one target *escapes* inactivation, but in the opposite sense, namely that the inactivation of any one of several targets is sufficient to destroy the cell's ability to proliferate. The algebraic expression for exponential survival, $\ln f = -kD$, could then be written:

$$\ln f = -(k_a + k_b + k_c \ldots)D \qquad (4)$$

We may use that expression to state in algebraic symbols the proposition that cell killing may be attributed to either of two classes of lesion: P and Q

lesions. Both of these may, of course, embody subclasses. Equation (3) may then be re-written:

$$\ln f = -(k_p + {}_1k_q)\, D + F(D) \quad . \quad . \quad . \quad (5)$$

k_p and ${}_1k_q$ being the inactivation constants for unrepaired P and Q lesions. The fraction of Q lesions initially repaired is defined as ${}_2k_q/{}_1k_q$ and $F(D)$ refers only to repair of Q lesions.

Sensitizing and Protective Agents

There are many agents that protect or sensitize cells, if they are present during irradiation. Their effect will be reflected by an appropriate change in the constants of the expression that represents the logarithm of the surviving fraction. If oxygen is used as an example, its effect might be predicted to be strictly "dose-modifying" or, a better term, "dose-multiplying". This is because experimental evidence supports the hypothesis that oxygen sensitizes by "fixing" damage: that is to say, it readily combines with radiation-induced radicals, only a fraction of which (say $1/m$) would otherwise fail to recapture their missing electrons. Oxygen therefore acts just as if the dose delivered has been multiplied by m, and this is the oxygen enhancement ratio. In any expression describing dose-effect relationships, each term involving dose (symbolized by the variable D) must then be multiplied by the same factor. Even if there are different components of the terms involving dose, as in equation (4), with different values of o.e.r. applicable to each, the overall effect of oxygen should still be dose multiplying.

With all multi-sublethal lesion models, the shape of the survival curve is determined by constants applied to the term D, so that the effect of a dose-multiplying agent is to yield a new curve which is superimposable on the unmodified one, if the dose scales are in the appropriate ratio. If the curves have exponential terminal regions, these will extrapolate to the same number (n, in an n-target model) on the zero dose axis, or, if not, tangents on the two curves at the same survival level will extrapolate to the same point. It has now become customary, in fact, to regard common extrapolation numbers for survival curves as not only necessary, but also sufficient evidence of dose-multiplication by *any* agent. Some experiments on the effect of oxygen (*e.g.* McNally, 1975) have yielded results in which initial and terminal slopes of the pair of survival curves are not modified by the same factor, even when the extrapolation numbers are not significantly different. Oxygen is then not strictly dose-multiplying and ancillary hypotheses have been suggested to account for this: for example, that the o.e.r. is less in the low-dose than in the high-dose region because an effect of the high LET component of low LET radiation can be detected in the initial region of the curve.

A repair model will, like the multi-sublethal lesions models, require n to be constant when a dose-multiplying agent is used, provided that the treatment does not change n in some way that is independent of its *dose*-multiplying effect. In repair models, the extrapolation number, n, derives its meaning from the assumption that, in a given set of conditions, there will be a fixed number of lesions per cell that can be repaired, but no assumption is involved as to whether that number may, or may not, be affected by a modifying agent. If it is, there is no *a priori* reason to suppose that the change is related to the dose-multiplying action of the agent in respect of the expression of reparable or irreparable lesions.

Equation (5) takes account of two categories of potentially lethal lesion. If it is correct, in principle, as a statement of the mode of cell killing, it may be used to show (1) that repair of P lesions (the phenomenon now known as "repair of potentially lethal damage") will appear to be "dose-multiplying", but only in the sense that n will remain unchanged, and (2) that differential effects of oxygen or of other agents on incipient P and Q lesions will lead to different enhancement or protection ratios for the initial and terminal slopes of pairs of survival curves (see Appendix).

Interpretation of some Radiobiological Phenomena

The plausibility of a repair model for cell killing, as represented by equations (3) or (5), will depend on how successful it is in accommodating observations concerned with Elkind recovery. Many experimental results might be examined in this light, and might reflect on the nature and mode of action of Q-factor and its recovery, on the basis of the relevant assumptions. One group of observations, in particular, could be satisfactorily accounted for on the simple proposal that the factor can diffuse through the plasma membrane and presumably, therefore, also through the nuclear membrane. Durand and Sutherland (1972), experimenting with "spheroids"—small groups of cells remaining in contact, *in vitro*, until separated by trypsin treatment—found that the cells irradiated in spheroids, when plated as single cells, yielded larger values of n than irradiated single cells of the same line, with the value of D_0 unchanged. The property that conferred the larger shoulder on the survival curve for spheroid cells was still present immediately after separation; but it diminished rapidly thereafter. Diffusion of Q-factor out of isolated cells could provide a neat explanation for those observations, and for the general experience that cells in organized tissues respond as if the extrapolation numbers to their survival curves were very much larger than for any mammalian cells irradiated *in vitro* (Withers, 1970; Alper, 1974a). Furthermore, there are instances of significant differences in values of n, depending on whether cells have been irradiated while fixed on a surface, or in suspension with constant stirring (Bryant, 1973). That phenomenon, and indeed the so far unexplained day-to-day variability of n for cells of the same line handled *in vitro* (*e.g.* Elkind *et al.*, 1961), are more easily interpreted in terms of a Q-lesion, diffusible Q-factor hypothesis than by invoking the multi-sublethal lesion concept.

Other experimental observations might likewise be more easily accommodated by a repair model; some of these were quoted by Orr *et al.* (1975). One group of results, in particular, have so far defied interpretation in terms of predictions from the oxygen fixation hypothesis, in the context of a multi-sub-lethal lesion concept: cells irradiated under "severe anoxia", or after a period of prolonged hypoxia, yield exponential survival curves, or curves with extrapolation numbers lower than those for the cells irradiated with oxygen present (Littbrand and Révész, 1969; Nias *et al.*, 1973). In terms of the Q-lesion, Q-factor hypothesis such a change in n might signify that the pre-irradiation treatment of the cells had wrought a change in the concentration of Q-factor, perhaps by its effect on cell membranes. If that were the case, it might be expected that cells exposed to severe anoxia, or prolonged hypoxia, would still demonstrate a lower value of n, even if irradiated aerobically, than if they had not been so treated before irradiation.

That changes in the nature of the nuclear and/or plasma membrane could, through affecting the local concentration of Q-factor, change the value of n for survival curves might, at least to some extent, be reflected in the change in radiation response through the mitotic cycle (Fig. 1). In general, survival curves are closest to an exponential form for cells in mitosis, when the nucleus is not defined by a membrane.

It is, of course, always possible to find existing experimental results that appear to be explained by, or to support, a postulated mechanism of action of radiation on cells. If the Q-factor hypothesis does indeed gain credibility from the further assumption that it can move out of cells, or between them, methods of direct experimental test should not be difficult to devise.

So far, only observations with radiations of low LET have been mentioned. Although the value of n varies greatly between cell lines, and varies also within the same line, according to the morphological and physiological state of the cells at the time of irradiation, it is a generality that most low LET survival curves for eukaryotic cells have shoulders, and that Elkind recovery results in "restoring the shoulder" to the survival curve for survivors of a first dose, even when that has been large. When radiation of higher LET is used, however, there is no generality about the mode of change in response. The only feature common to nearly all cells is that biological effectiveness increases with increasing LET; but there is no constant pattern of change. If we consider only mammalian cells, and only two qualities of radiation—fast neutrons and X rays—we find that there are apparently fundamental differences in the way survival curves are modified by the change in LET. In some cases the extrapolation number is the same (*e.g.* Hornsey and Silini, 1961; Nias and Gilbert, 1975): the RBE of neutrons is equal to the ratio of slopes of the survival curves. At the other extreme, terminal slopes are almost the same, the whole of the increased RBE being attributable to a much lower n for the neutron survival curve (*e.g.* Withers *et al.*, 1970). Similarly, there are differences in the operation of Elkind recovery. With some test systems it is complete within about the same time after neutron as after X-irradiation, and its extent matches the shoulder of the neutron survival curve (Hornsey and Silini, 1962; Withers *et al.*, 1970). In contrast, Durand and Olive (1977) could detect no Elkind recovery up to six hours after neutron irradiation of V79 hamster cells, although there were pronounced shoulders in the neutron survival curves, and n was greater for cells irradiated in spheroids than singly, just as had been observed with X rays (Durand and Sutherland, 1972).

Such conflicting results are impossible to interpret in terms of any one of the current multi-sublethal lesion models, and would be difficult also to accommodate by a repair model, at any rate one that is presented in as simple a form as has been cited here. Some consideration must, however, be given to the basic fact that RBE does increase with increasing LET. Theory predicts that effectiveness must *decrease* with increasing LET when inactivation results from single energy deposition, since a second event within the same target would be without effect. The prediction has been verified for model "targets" irradiated extracellularly, such as double-stranded DNA viruses (*e.g.* Schambra and Hutchinson, 1964; Christensen *et al.*, 1972). But, in terms of the repair model, cell inactivation need be attributed only to "single-hit" action on any one cellular target: if that is tenable, increasing RBE requires to be explained. As I have previously suggested (Alper, 1974b), this apparently paradoxical result would be produced if adjoining targets could effect mutual repair. Single energy deposition events spaced far apart would then have less effect than if the two adjacent targets—nuclear membrane and attached DNA, for example—were damaged together in the passage of a single ionizing particle. Alternatively, or perhaps in addition, it might be envisaged that *Q*-lesions, in particular, are rendered the less capable of repair, the greater the amount of energy deposited within the target volume in the passage of a single particle. That intracellular lesions are less reparable if engendered by radiation of high than of low LET has, of course, often been suggested; but it is a difficult hypothesis to test.

Further experimentation will show whether the "multi-sublethal lesion" or the "repair" models are better able to account for RBE effects, which are evidently closely linked with Elkind recovery. It is important that one or other of these fundamentally different types of model be validated, because experimental approaches to practical as well as basic problems are always to a large extent determined by a conceptual framework. While the problems posed by Elkind recovery are certainly of clinical importance, the phenomenon itself, together with the "shoulder" on which it rests, is crucial to our understanding of the radiobiology of mammalian cells.

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APPENDIX

COROLLARIES OF THE *Q*-FACTOR, *Q*-LESION HYPOTHESIS

(a) *Repair of* P *lesions (customarily known as "repair of potentially lethal damage")*

This repair capacity is assumed not to decrease with increasing dose. For simplicity, it is assumed that the repair of *Q* lesions, mediated by *Q*-factor, and repair of *P* lesions occur independently. In equation (5),

$$ln\ f = -(K_\mathrm{p} + {}_1K_\mathrm{q})\ D + F(D)$$

$F(D)$ relates only to repair of the potentially lethal *Q* lesions, and determines the extrapolation number n. In conditions in which repair of *P* lesions occurs, let ${}_1K_\mathrm{p}$ incipient *P* lesions be engendered per unit dose, and let a fraction ${}_2K_\mathrm{p}/{}_1K_\mathrm{p}$ of these be repaired.

The low dose approximations of equation (5), with and without repair of *P* lesions, are respectively

$$ln\ f = -({}_1K_\mathrm{p} + {}_1K_\mathrm{q} - {}_2K_\mathrm{p} - {}_2K_\mathrm{q})D$$

and $ln\ f = -({}_1K_\mathrm{p} + {}_1K_\mathrm{q} - {}_2K_\mathrm{q})D$

giving, as ratio of initial slopes,

$$\frac{{}_1K_\mathrm{p} + {}_1K_\mathrm{q} - {}_2K_\mathrm{p} - {}_2K_\mathrm{q}}{{}_1K_\mathrm{p} + {}_1K_\mathrm{q} - {}_2K_\mathrm{q}} = R_i$$

The corresponding high dose approximations are:

$$ln\ f = -({}_1K_\mathrm{p} + {}_1K_\mathrm{q} - {}_2K_\mathrm{p})D + ln\ n$$

and $ln\ f = -({}_1K_\mathrm{p} + {}_1K_\mathrm{q})D + ln\ n$

Thus the ratio of the final slopes is

$$\frac{{}_1K_\mathrm{p} + {}_1K_\mathrm{q} - {}_2K_\mathrm{p}}{{}_1K_\mathrm{p} + {}_1K_\mathrm{q}} = R_f$$

Since R_i and $\mathrm{R_f}$ are both < 1, $\mathrm{R}_f > R_i$. Thus, with repair of *P* lesions, the final slope will change to a lesser extent than the initial slope. The extrapolation number will be unchanged.

(b) *Effect of a dose-multiplying agent which acts differently on* P *and* Q *lesions*

Let the dose-multiplying constants be m_p and m_q for *P* and *Q* lesions respectively.

The low dose approximations, with and without the operation of the agent, will be respectively:

$$ln\ f = -(m_\mathrm{p}K_\mathrm{p} + m_\mathrm{q}\ .\ {}_1K_\mathrm{q} - m_\mathrm{q}\ .\ {}_2K_\mathrm{q})D$$

and $ln\ f = -(K_\mathrm{p} + {}_1K_\mathrm{q} - {}_2K_\mathrm{q})D$,

so the apparent dose multiplying factor for the agent will be

$$\frac{m_\mathrm{p}K_\mathrm{p} + m_\mathrm{q}\ .\ {}_1K_\mathrm{q} - m_\mathrm{q}\ .\ {}_2K_\mathrm{q}}{K_\mathrm{p} + {}_1K_\mathrm{q} - {}_2K_\mathrm{q}} = DMF_\mathrm{i}$$

the corresponding high dose approximations will be:

$$ln\ f = -(m_\mathrm{p}K_\mathrm{p} + m_{\mathrm{q}2}K_\mathrm{q})D + ln\ n$$

$$ln\ f = -(K_\mathrm{p} + {}_1K_\mathrm{q})D + ln\ n,$$

the extrapolation number remaining constant, *provided the agent has no (independent) effect upon the repair mechanism that determines n.* The apparent dose multiplying factor at high dose will be

$$\frac{m_\mathrm{p}K_\mathrm{p} + m_\mathrm{q}\ .\ {}_1K_\mathrm{q}}{K_\mathrm{p} + {}_1K_\mathrm{q}} = DMF_\mathrm{f}$$

If m_p and m_q are both >1, and if $m_\mathrm{p} \neq m_\mathrm{q}$, the apparent dose multiplying factors will not be the same in the initial and final regions of the pair of survival curves.

Let m_p be greater than m_q, *i.e.* $m_\mathrm{p} = m_\mathrm{q} + \triangle$.

$$DMF_\mathrm{i} = m_\mathrm{q} + \frac{\triangle K_\mathrm{p}}{K_\mathrm{p} + {}_1K_\mathrm{q} - {}_2K_\mathrm{q}}$$

and $DMF_\mathrm{f} = m_\mathrm{q} + \dfrac{\triangle K_\mathrm{p}}{K_\mathrm{p} + {}_1K_\mathrm{q}}$

$\therefore$ The *DMF* applying to the initial regions will be the greater.

Conversely, if $m_q > m_p$, the *DMF* applying to the initial regions will be less than that applying to the final ones. The extrapolation number would be unchanged if the agent did not change the effectiveness with which *Q* lesions were repaired.

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Observations on the behaviour of barium sulphate suspensions in gastric secretion*

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ABSTRACT

A number of barium sulphate suspensions showed varying patterns of stability when provoked with gastric secretion. The stability of the suspensions was affected by the pH, the mucin content and the volume of secretion used. These studies indicate that flocculation of the suspension in the presence of gastric residue decreases as the amount of undiluted barium sulphate in the mixture is increased.

The nature and composition of barium sulphate suspensions, factors producing flocculation, and the value of additives in improving stability and mucosal coating have been extensively reviewed in the literature (Knoefel *et al.*, 1956; Brown, 1963; Miller, 1965; Embring and Mattsson, 1968; Sellink, 1971; Miller, 1973).

The instability of some suspensions in the presence of gastric residue results in failure to coat the mucosa adequately for detailed double contrast examination (Fig. 1). In this study the stability and flocculation patterns of certain proprietary barium sulphate suspensions have been investigated, and methods whereby stability could be achieved or restored were studied.

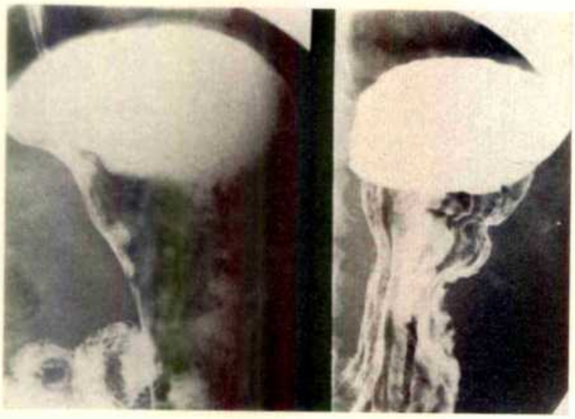
A B

FIG. 1.

Barium studies in the same patient, (A) with gastric residue, and (B) one week later with no gastric residue when the examination commenced.

MATERIALS AND METHODS

The following barium sulphate suspensions were studied—Micropaque (Nicholas), Baritop (Concept Pharmaceuticals), Liquibarine (Norgine), Barosperse (Mallinckrodt), E-Z-Paque (E-Z-EM Company), and barium sulphate suspended in sorbitol (Embring and Mattsson, 1968). The suspensions were prepared in accordance with the instructions of the manufacturers.

The following four tests were used to assess the stability patterns of these suspensions.

1. *The effect of pH, mucin and pepsin on flocculation*

In a series of eight test tubes, was placed 8 ml of one of the following test agents—N/10 hydrochloric acid, human gastric secretion at pH 1.5, the same secretion buffered to pH 3, 4.5, 6 and 7.5 with sodium bicarbonate, sodium bicarbonate itself, and normal saline (Table I). To each of these tubes 2 ml of the same barium sulphate suspension was added. After thorough mixing of the contents of each tube, they were allowed to stand and horizontal beam radiographs were taken immediately after shaking and five minutes later. Preliminary testing showed that at five minutes flocculation, if present, was clearly detectable so that further delayed films were not necessary. Flocculation and settling of the suspensions was apparent from examination of the radiographs. Each barium was tested in this way at least three times.

Tubes 1, 2, 4 and 7 (Fig. 2) were then re-shaken and thin smears of each mixture were made on clean uncontaminated microscope slides. The slides were photographed on X-ray film and the failure or otherwise of the barium to form a thin uniform film was noted (Fig. 3).

Subsequently each barium sulphate suspension was tested in identical fashion against simulated

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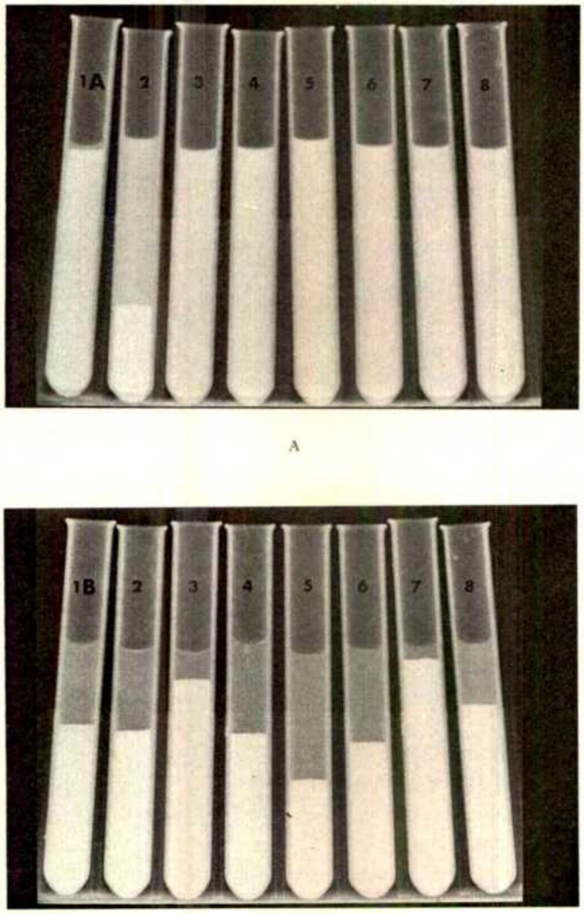
* Based on a paper read to a combined meeting of The British Institute of Radiology, Faculty of Radiologists, and the Royal Society of Medicine (Radiology Section) at the Royal College of Surgeons of England, in January 1975.

TABLE I

THE EFFECT OF pH ON THE STABILITY OF BARIUM SULPHATE SUSPENSIONS

Tube number and contents	Micropaque	Baritop	Liquibarine	Barosperse	E-Z-Paque	Barium sulphate and sorbitol
1. N/10 HCl	S	F	F	F	F	F
2. Gastric juice at pH 1.5	Variable	F	F	F	F	F
3. pH 3.0	S	S	S/S	F	S	F
4. pH 4.5	S	S	S/S	S	S	F
5. pH 6.0	S	S	S/S	S	S	F
6. pH 7.5	S	S	S/S	F	S	F
7. Sodium bicarbonate (pH 8.2)	F	S	S/S	F	F	F
8. N. saline	S	S	S/S	F	S	F

S = Stable. F = Flocculation. S/S = Stable with sediment.



A

B

FIG. 2.

Method of testing stability of barium sulphate suspensions. The eight agents used to provoke the suspensions are listed in Table I. Series A shows the stability pattern of Baritop with a wide range of resistance to flocculation. In Series B Barosperse has flocculated throughout. Each tube contains 8 ml of provoking agent and 2 ml of barium suspension.

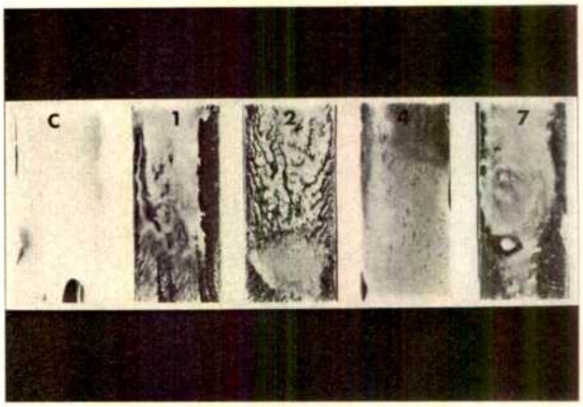


FIG. 3.

Thin film smears showing effect of flocculation on thin film quality. C denotes undiluted and unprovoked barium sulphate suspended in sorbitol. The four slides show the thin smears produced by samples from tubes 1, 2, 4 and 7 in Table I.

gastric juice*, and simulated gastric juice from which first mucin and then pepsin had been omitted during preparation.

2. *Threshold of flocculation in relation to the volume of gastric secretion*

In this test the volume of barium suspension in relation to the volumes of human gastric juice (at pH 1.0–1.5) was progressively increased to assess whether increasing volumes of barium suspension influenced stability. The tubes were again radiographed and thin smear slides obtained. Each barium suspension was tested at least three times.

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[*] The simulated gastric juice was based on the U.S.P. formula and consisted of sodium chloride 2 g, pepsin 3.2 g, Mucin 1 g, hydrochloric acid 7 ml and water up to 1 litre.

TABLE II

THRESHOLD OF FLOCCULATION OF BARIUM SULPHATE SUSPENSIONS

Ratio of gastric juice to barium by volume (ml)	Micropaque	Baritop	Liquibarine	Barosperse	E-Z-Paque	Barium sulphate and sorbitol
8/2	F	F	F	F	F	F
7/3	F	F	S	F	F	S
6/4	F	F	S	S	S	S
5/5	F	F	S	S	S	S
4/6	S	S	S	S	S	S

S = Stable. F = Flocculation.

TABLE III

THE pH OF BARIUM SULPHATE AND ITS RESISTANCE TO FLOCCULATION

(pH of the human gastric juice used = 1.1*)

Barium suspension	pH before mixing	Volume of barium to juice					
		1:4		1:1		4:1	
		pH	Stability	pH	Stability	pH	Stability
Micropaque	5.1	1.4	F	1.5	F	3.4	S
Baritop	5.2	1.9	F	2.9	F	4.1	S
Liquibarine	9.8	3.7	F	6.4	S	9.3	S
Barosperse	6.9	1.2	F	1.5	S	1.8	S
E-Z-Paque	6.6	1.2	F	1.7	S	3.9	S
Barium with sorbitol	7.2	1.7	F	4.5	S	5.7	S

*Pye Unicam pH meter.

The pH of each barium suspension tested was noted and also the pH of the mixture of barium suspension and gastric juice.

3. *Effect of dilution on stability*

The barium sulphate suspensions were diluted with water to 75%, 50% and 25% of the recommended concentration and each suspension was tested for stability against N/10 hydrochloric acid, human gastric juice at pH 1.0–1.5, sodium bicarbonate and normal saline. Equal volumes of barium and the above agents were used as it was found that a 1:4 mixture by volume of barium to gastric secretion rendered the radiographic density of the mixture at 25% recommended concentration too low to be assessed by this technique.

4. *Adsorption of the factor causing flocculation*

Two ml of each undiluted barium sulphate suspension in turn were added and thoroughly mixed with 8 ml aliquots of gastric juice at pH 1.5. When flocculation and separation occurred 8 ml of the clear supernatant were transferred to a second tube. To this a further 2 ml of the original barium suspension were added and the behaviour of the mixture was noted.

RESULTS

The results of these tests are shown in Tables I to V.

1. *The effect of pH, mucin and pepsin on flocculation*

There was wide variation in the behaviour of the barium suspensions when mixed with the agents enumerated in Table I. In the proportions used, Micropaque was the only stable suspension in N/10 hydrochloric acid. All the suspensions tested were unstable in human gastric secretion at pH 1.0–1.5. Micropaque and Baritop were stable at a wider range of pH than Barosperse and E-Z-Paque. Barosperse and barium sulphate suspended in sorbitol flocculated in normal saline.

Simulated and human gastric juice gave identical results. When mucin was omitted from simulated gastric juice, Micropaque, Baritop, and Liquibarine remained stable even at a pH of 1.0–1.5. However, there was no change in the stability patterns of Barosperse, E-Z-Paque and barium sulphate in sorbitol when mucin was omitted during preparation.

TABLE IV

THE EFFECT OF DILUTION WITH WATER ON THE STABILITY OF BARIUM SULPHATE SUSPENSIONS

	Micropaque				Baritop				Liquibarine				Barosperse				E-Z-Paque				Barium sulphate and sorbitol			
	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)
N/10 HCl	S	S	S	S	S	S	F	F	S	F	F	F	S	S	F	F	S	F	F	F	S	S	S	F
Gastric juice (pH 1.5)	S	S	S	S	S	S	F	F	S	F	F	F	S	F	F	F	S	S	F	F	S	S	S	F
Normal sodium bicarbonate	S	S	S	S	S	S	S	S	S	F	F	F	S	S	F	F	S	S	F	F	S	S	S	F
Normal saline	S	S	S	S	S	S	S	S	S	F	F	F	S	F	F	F	S	S	S	F	S	S	S	F

S = Stable. F = Flocculation.
(a) Undiluted barium sulphate.
(b) 75%
(c) 50% } recommended concentration after addition of water.
(d) 25%

TABLE V

ADSORPTION OF THE FACTOR CAUSING FLOCCULATION
(Using gastric juice at pH 1.5)

	1st tube	2nd tube
Micropaque	F	S
Baritop	F	S
Liquibarine	F	S/F
Barosperse	F	F
E-Z-Paque	F	F
Barium sulphate/sorbitol	F	F

S = Stable. F = Flocculation.

Omitting pepsin from the simulated juice made no difference to the pattern of stability in any of the barium suspensions tested.

2. *Threshold of flocculation*

Table II shows that with Micropaque and Baritop larger volumes of the suspension than of gastric juice were required to prevent flocculation. Liquibarine and barium sulphate suspended in sorbitol however remained stable at a much lower concentration in gastric juice and Barosperse and E-Z-Paque formed an intermediate group. Table III shows the relationship between pH of the original barium suspension, the pH of the mixture at different concentrations of each barium suspension in gastric juice, and the resistance to flocculation. The more alkaline the initial pH of the barium suspension the more resistant it is to flocculation in terms of volume of barium to gastric juice, and vice versa, irrespective of the pH of the eventual mixture of barium and juice. For instance, with equal volumes of Baritop and gastric secretion there was flocculation at pH 2.9 whereas Barosperse and E-Z-Paque were stable at pH 1.5 and 1.7 respectively, although the latter were less acid in their original suspension than Baritop.

3. *Effect of dilution on stability*

All the barium suspensions tested with the exception of Micropaque showed an increasing susceptibility to flocculation by gastric secretion when diluted with water. Liquibarine and Barosperse were particularly unstable when diluted, in all the provoking media (Table IV).

4. *Adsorption of the factor causing flocculation*

Micropaque and Baritop both exhibited a phenomenon whereby gastric juice could be "treated" with a small volume of that barium suspension and thus rendered incapable of flocculating additional amounts of the same barium provided the flocks produced initially were removed from the mixture (Table V). The results with Liquibarine were variable.

DISCUSSION

The physical properties of barium sulphate suspensions have been reviewed by Brown (1963), Sellink (1971), and Miller (1965; 1973). Factors affecting their stability have been enumerated—barium particle size, nature of the suspending agents, mucin in gastric secretion. The importance of dilution with water and of the role of mucin in producing flocculation was stressed by Knoefel *et al.* (1956). Additives such as carboxymethylcellulose and sorbitol have been used in an attempt to improve the stability of these suspensions (Knoefel *et al.*, 1956; Embring and Mattsson, 1968).

We have limited our investigations to the ability of suspensions to resist flocculation in gastric secretion and have not investigated other properties of the suspensions such as density, viscosity, palatability, formation and retention of bubbles and the settling rate of unprovoked suspensions on standing. This study was prompted by the finding during tubeless double contrast studies of the stomach that some barium suspensions gave better mucosal detail and coating than others particularly in the presence of gastric residue.

The tests used were designed to assess the susceptibility of barium suspensions to flocculate in various media and to determine what factors were responsible for such instability. There was wide variation in stability between the various barium suspensions tested; the mechanisms accounting for flocculation probably differ between suspensions and are poorly understood. The manufacturers of barium sulphate suspensions are reluctant to divulge the precise constituents of their preparations (Miller, 1965).

Nevertheless, the results indicate that the tendency to flocculate could be improved by increasing the amount of undiluted barium used. The undesirable flocculating effect of gastric secretion can be "swamped" by using more barium suspension so that mucosal coating and detail is improved. The relative volumes of barium to gastric secretion necessary to do this, differ from preparation to preparation (Table II).

The relationship between the pH of the barium sulphate suspension and its resistance to flocculation is interesting. The less acid the pH of the barium the greater its resistance (Tables II and III) despite the fact that the pH of the eventual mixture of barium and gastric juice may remain acid (Table III). This paradox is difficult to explain and is the subject of further investigation.

The two preparations that are capable of adsorbing the factor causing flocculation from gastric secretion, Micropaque and Baritop, both require larger volumes to attain stability (Tables II and IV). However, both preparations are resistant to flocculation through a wide range of pH (Table I) but differ markedly in their stability when they are diluted with water—Micropaque being far superior in this respect (Table IV).

Acknowledgments

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Sellink, J. L., 1971. In *Examination of the Small Intestine by means of duodenal intubation* (Stenfert Kroese, Leiden).

Book review

Ultrasound in Medical Diagnosis. By D. N. White, pp. 329. Illus., 1976, (Canada, Ultramedison), $35.00.

This book is intended as an introduction for non-physicists to the basic physical principles of medical ultrasound. Because of its admirable avoidance of complex physics numerous similies are made but, in general, are successful in their aim and the chapters on elementary acoustics, the generating system and the receiving system will be most valuable to those wishing to learn about these subjects. Chapter 1 is a well informed and fascinating historical review, often based on the author's personal acquaintance with the characters described.

The author states in his introduction that he has made no attempt to cover the clinical aspects of ultrasound and one is prepared to accept this only to find Chapter 5, Imaging Systems, filled with a miscellany of research orientated clinically unproven systems such as transmission techniques, time delay spectrometry, acoustic holography and acoustic microscopy. This chapter also contains a rather ill-informed critique of computerized X-ray tomography which must have been based on superficial knowledge of a very early scanner when "patients had to lie completely still during the ten minutes or so necessary to complete the scanning". Whilst this chapter could be interesting it is based upon a review of the literature rather than personal knowledge and is out of place in this book and would be better placed in a book on clinical applications.

The final chapter is a general review of imaging as a concept and covers a wide range of subjects not related to the prime object of the book. Whilst this may also be interesting it would probably have been better in a more condensed form and used as an introduction rather than a conclusion.

One would purchase this book primarily as an introductory text to the principles of ultrasound and it can be recommended as such.

H. B. Meire

1977, *British Journal of Radiology*, *50*, 473–482 JULY 1977

Pseudoachondroplasia, a report of 13 cases

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ABSTRACT

Pseudoachondroplasia is a heterogeneous inherited skeletal dysplasia in which dwarfism is a major feature. Affected individuals have a normal craniofacial appearance and the skeletal malformations do not become apparent until early childhood. Radiographic changes observed in 13 affected individuals include shortening of tubular bones, flaring of metaphyses, variable epiphyseal maldevelopment and some degree of vertebral end-plate malformation. Diagnostic precision is essential for effective management and genetic counselling.

Pseudoachondroplasia, a relatively common form of short-limbed dwarfism, is usually recognized in early childhood, after the development of disturbances of gait or deformity of the knee joints. Clinical features include joint laxity, limitation of extension of the elbows, genu varum or genu valgum and moderate lumbar lordosis. The facies, intelligence and life span are normal.

The entity of pseudoachondroplasia was delineated from classical achondroplasia and the spondyloepiphyseal dysplasias by Maroteaux and Lamy (1959). Ford *et al.* (1961) subsequently described three affected individuals and since that time, more than 50 cases have been reported.

Recognizing the heterogeneity of the disorder, Hall and Dorst (1969) divided pseudoachondroplasia into four types. Although this classification is not universally accepted, there is little doubt concerning the existence of autosomal dominant and autosomal recessive forms of the condition. In this context, diagnostic precision is important, otherwise genetic counselling is unrealistic and inaccurate.

We have investigated 13 patients with pseudoachondroplasia, included two kindreds with undoubted autosomal dominant inheritance and two siblings with a recessive form of the disorder. To facilitate recognition of the dominant and recessive types of pseudoachondroplasia, we describe, depict and discuss the clinical and radiographic features of these individuals in this presentation.

PATIENTS AND METHODS

Since 1972, 13 individuals with pseudoachondroplasia have been investigated by the Department of Human Genetics, Cape Town, and their X-ray features independently assessed by the radiological staff. The ages of the patients varied from three to 30 years, 11 were in the growth period (under 18 years) and the others were 22 years and 30 years of age respectively. Patients with atypical features, or those in whom there was any doubt concerning the diagnosis, have been excluded from this review.

In one kindred, a mother and her son and daughter, were affected, while in another, a father and two sons had the condition. In a third kindred two affected brothers had normal siblings and parents (Fig. 1). The other patients were sporadic, having no affected kin. Pertinent data are summarized in Table I.

Detailed case reports of three individuals in the family with autosomal dominant inheritance and two brothers with autosomal recessive transmission of the condition are given. A sporadic patient with important clinical features is also described (Fig. 2).

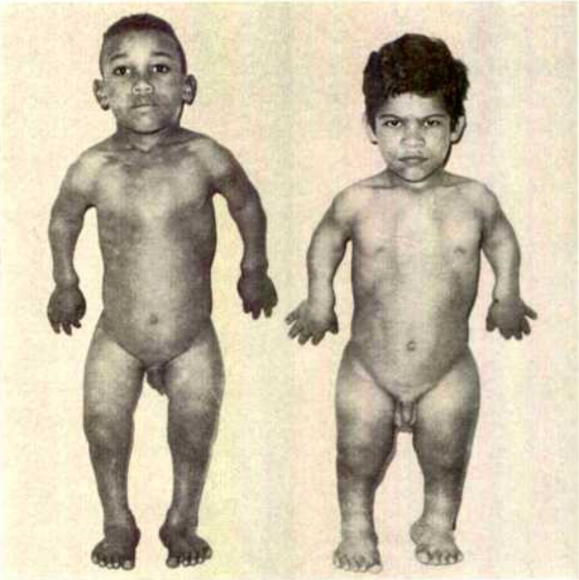

FIG. 1. *Case 4 and 5.*

The normal facies and pronounced short limbed dwarfism, with rhizomelic predominance, are apparent.

TABLE I

Pseudoachondroplasia—the patients in the series

Case	Year of birth	Sex	Race*	Age of clinical presentation	Age when examined	Height when examined (cm)	Presenting feature	Type of pseudoachondroplasia
Kindred 1								
1	1943	F	W	5	30	104	Genu valgum	AD mild
2	1966	F	W	6	6		Disturbed gait	AD mild
3	1969	M	W	3	3		Genu varum	AD mild
Kindred 2								
4	1956	M	C	8	16	91.5	Talipes e.v. Genu varum	AR severe
5	1962	M	C	7	10	91	Genu varum	AR severe
Sporadic patients								
6	1950	F	W	2	22	108	Quadriplegia at two Scoliosis at four	Severe—AD?
7	1966	F	A	10	10	96	Genu varum (gross)	Mild
8	1967	F	A	4	6	90	Genu varum	Mild
9	1970	F	W	2	3	86	Disturbed gait Genu varum	Severe
10	1964	M	A	4	8	88	Genu varum	Severe—AR?
11	1967	M	C	6	9	108	Genu varum	Mild—AR?
Kindred 3								
12	1965	M	I	11	11	—	Disturbed gait	AD mild
13	1970	M	I	6	6	—	Disturbed gait	AD Mild (father known to be affected —not examined) but radiographically evaluated

*I = Indian; A = African; C = Coloured; W = White.

General Features

1. *Clinical features*

The 13 patients were all normal at birth and in each instance deformity of the legs or disturbance of gait drew attention to the disorder in early childhood. Disproportionate dwarfism thereafter became increasingly apparent. In every patient, general health was good, intelligence was unimpaired, the head and face were normal, and there was no evidence of any extra-skeletal ramification. Stubby digits and joint laxity were notable features.

2. *Radiographic features*

The pertinent radiographic features were as follows:

(a) Skull radiographs were normal in all 13 patients.

(b) The tubular bones were shortened (severe in eight patients). This shortening was predominantly rhizomelic.

(c) Some epiphyseal irregularity with delayed maturation was present in all patients who were seen during the growth period (severe in five of these 11 patients).

(d) The hands and feet manifested shortening and widening of phalanges, metacarpals and metatarsals. Severe changes were present in seven patients. The "trident" configuration of the hands, which is a prominent feature of classical achondroplasia, was not encountered.

(e) Defective ossification of the vertebral end-plates led to some degree of deformity. These changes were very variable in degree. In childhood, mild and severe cases had respectively lesser and greater vertebral abnormalities. These consisted of rounded upper and lower margins of the vertebral bodies, platyspondyly, disc space widening and anterior tonguing. Severe changes were present in four of the 11 pre-adult cases. Of the two affected adults, both had mild platyspondyly, while one had in addition a severe scoliosis. There was no caudal diminution of the interpedicular distances in the lumbar vertebrae. However, the majority of the patients had some degree of exaggerated lumbar lordosis.

(f) Pelvic changes were non-specific, dysplasia of the acetabulum and absence of normal iliac flaring being the most obvious abnormalities.

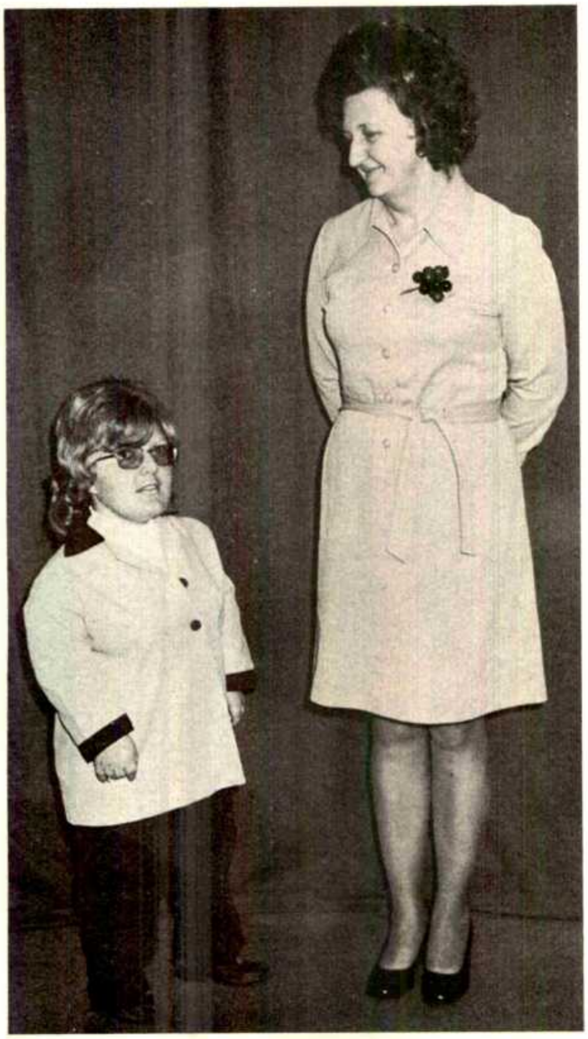

FIG. 2. *Case 6.*

Age 22 with her unaffected mother. Short limbed dwarfism and typically normal craniofacial appearance.

Cytogenic studies and routine biochemical investigations consistently yielded normal results. In particular, no patients had excessive urinary excretion of mucopolysaccharides.

In order to illustrate the features of the disorder, the clinical and radiographic manifestations of six of these 13 patients are described below.

CASE REPORTS

Kindred 1 (autosomal dominant—mild form)

The affected members of this kindred were a white female of British stock and her two offspring. The proband's father and mother, who were unaffected and non-consanguineous, had been aged 30 and 25, respectively, at the time of her birth. Her younger sister was normal but her own three-year-old son and six-year-old daughter were both affected. Her husband was unaffected.

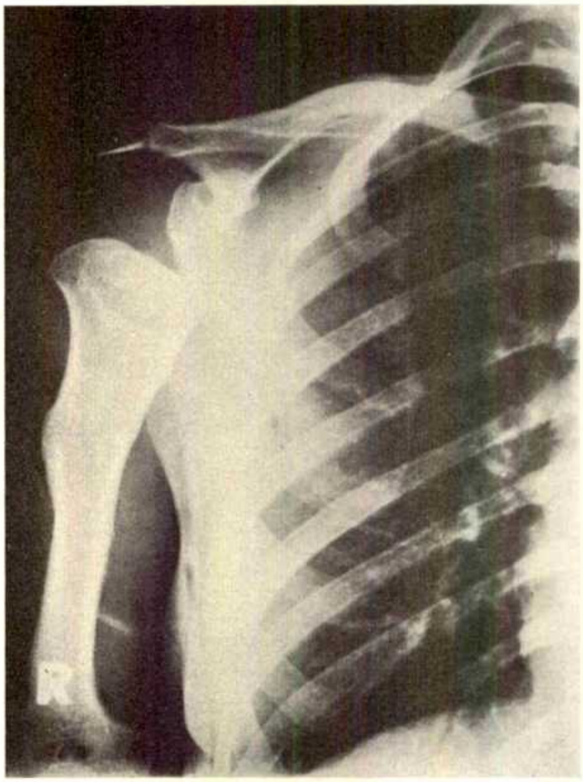

FIG. 3. *Case 1.*

Age 30 years. Marked shortening of the humerus, flattening of the humeral head and glenoid dysplasia are present.

Case 1

G.B., the proband, born in 1943, developed knock-knees when she was five years of age. Short stature was then recognized and a misdiagnosis of achondroplasia was made. Tibial osteotomy was undertaken at the age of nine years. In 1974, following the development of secondary osteoarthrosis, prosthetic replacement of the hip joints was successfully carried out. Similar procedures involving the knee joints are now contemplated. Cephalopelvic disproportion necessitated Caesarian section for delivery of her children.

At the time of the examination in 1973, the patient was 104 cm in height, with a span of 99 cm. She had a mild lumbar lordosis, proximal shortening of the limbs and stubby digits. The joints of the hands were hypermobile and the elbows lacked 20 deg. of extension. Her facies, hair, teeth and nails were normal.

On radiographic examination, the skull and spine proved to be normal. The tubular bones of the upper limbs were shortened with rhizomelic predominance. The humeral heads were expanded and flattened and the glenoid cavities were dysplastic (Fig. 3). The distal radial metaphyses sloped medially and the distal ulna was subluxated. There was slight bowing of these bones, with prominence of the radial tuberosities. The proximal row of carpal bones had a triangular configuration, and the metacarpals and phalanges were shortened.

The pelvis showed mild acetabular dysplasia and underdevelopment of the ilia (Fig. 4). In the femora, the necks and shafts were short, with coxa vara and distorted irregular heads. The metaphyses of the distal femora and proximal tibiae were flared (Fig. 5) and the sequelae of the previous

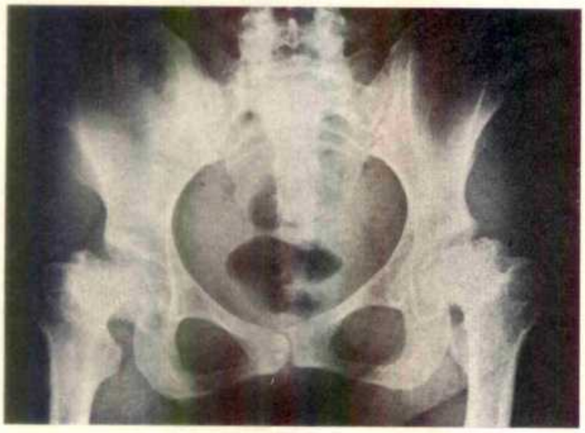

Fig. 4. *Case 1.*

Age 30 years. The acetabula are dysplastic and the femoral heads widened and flattened with changes of secondary osteoarthrosis. The ilia are underdeveloped. Severe coxa vara is present.

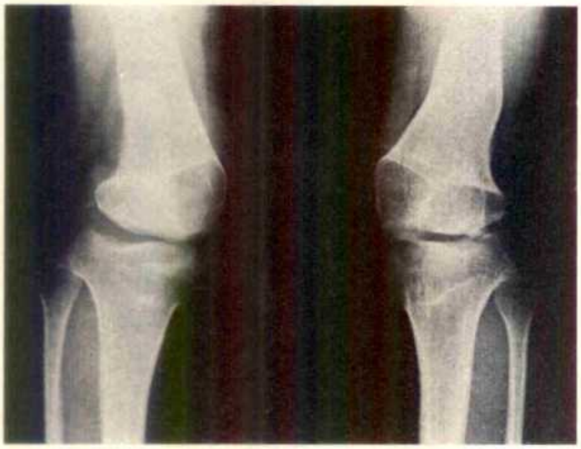

Fig. 5. *Case 1.*

Age 30 years. The distal femora and proximal tibiae are flared. Evidence of the previous tibial osteotomies is seen.

tibial osteotomies were evident. The fibulae were disproportionately long, both proximally and distally. In the ankle, slight medial tilt of the talus was present. The metatarsals were short, with flattened heads. Degenerative osteoarthrosis was a prominent feature, particularly in the weight-bearing joints.

Case 2

L.D., the proband's eldest daughter, born in 1966, noticed difficulty in running when she was six years of age. At the time, she was somewhat shorter than her peers, but she was otherwise normal. The diagnosis of pseudoachondroplasia was confirmed following radiographic studies in 1973.

Radiographs revealed rounding of the upper and lower margins of the vertebral bodies (Fig. 6). In the pelvis, acetabular dysplasia was a striking feature. The femoral capital

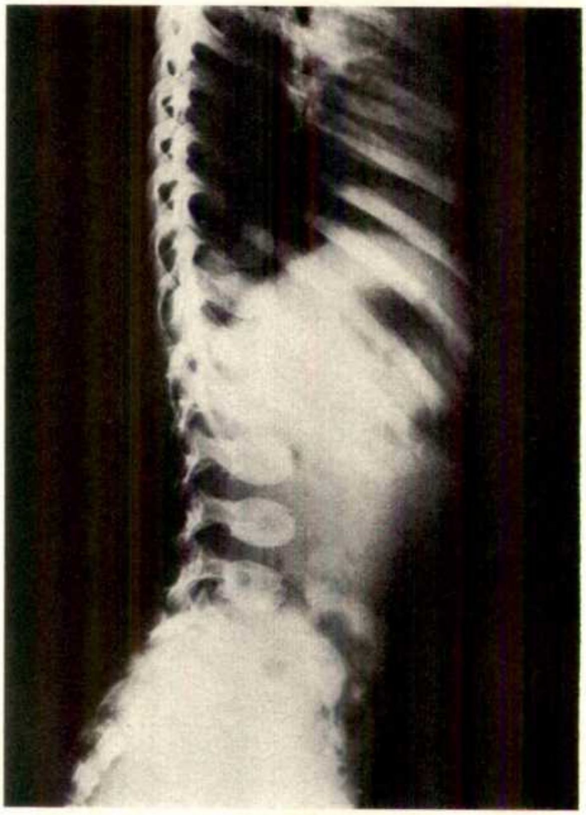

Fig. 6. *Case 2.*

Age seven years. Rounding of the upper and lower surfaces of the lumbar vertebral bodies with mild anterior tonguing is evident.

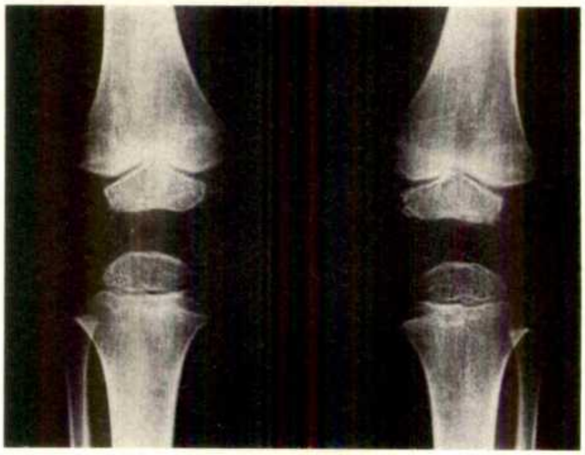

Fig. 7. *Case 2.*

Age seven years. Mild flaring of the distal femoral and proximal tibial metaphyses is evident. The distal femoral epiphyses are triangular, fitting in central notches in the femoral metaphyses.

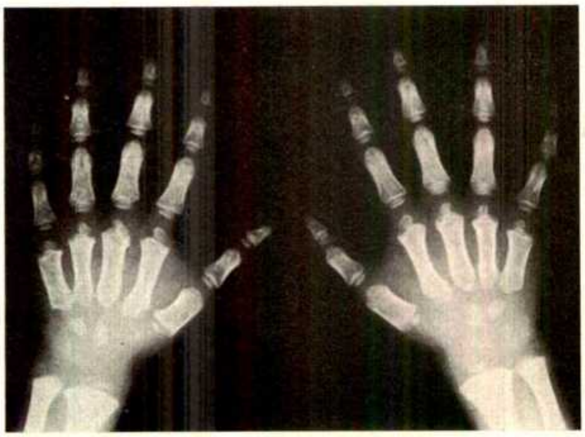

FIG. 8. *Case 2.*
Age seven years. There is shortening and widening of the phalanges and metacarpals. The carpals are immature and of irregular configuration.

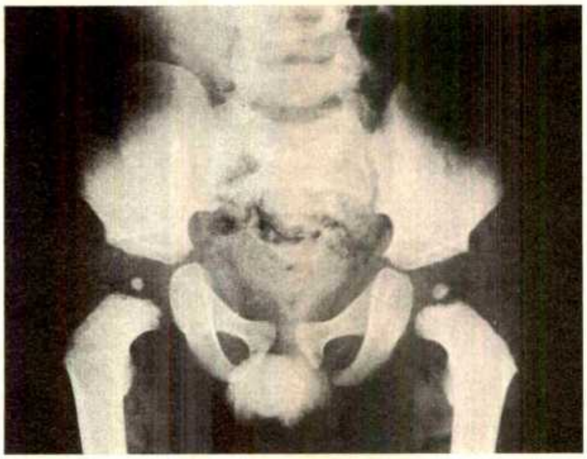

FIG. 9. *Case 3.*
Age three years. The acetabula are dysplastic and the proximal femoral epiphyses are markedly underdeveloped. Platyspondyly of the lower lumbar vertebral bodies is also evident.

epiphyses were small, while the distal epiphyses were triangular in shape fitting into a central metaphyseal notch (Fig. 7).

In the upper limbs cubitus valgus was evident with immature uneven humeral epiphyses and irregular and slightly flared metaphyses. In the wrists, underdeveloped and misshapen carpal bones were a striking feature. The phalanges were foreshortened, and proximal narrowing of the metacarpals was present (Fig. 8).

P.D., the son of the proband, born in 1969, developed knock-knees at the age of three. He was otherwise normal, but the diagnosis of pseudoachondroplasia was confirmed radiographically at this time.

The radiographic changes closely resembled those of his sister, the skull being normal, while the vertebral bodies had anterior tonguing and rounded upper and lower margins.

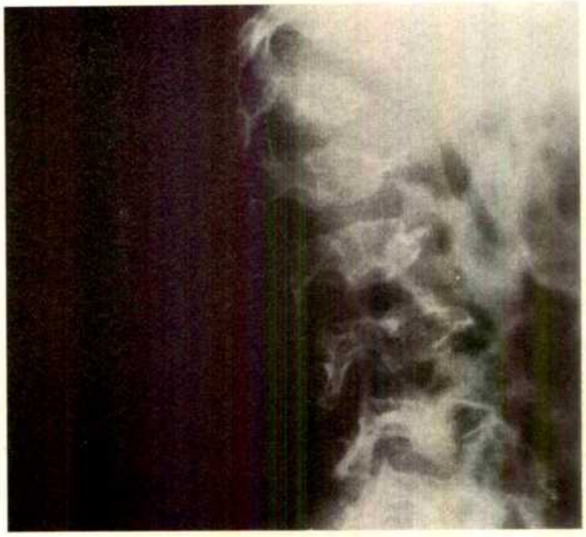

FIG. 10. *Case 4.*
Age eight years. The platyspondyly and "bellows" vertebrae with marked anterior tonguing are seen.

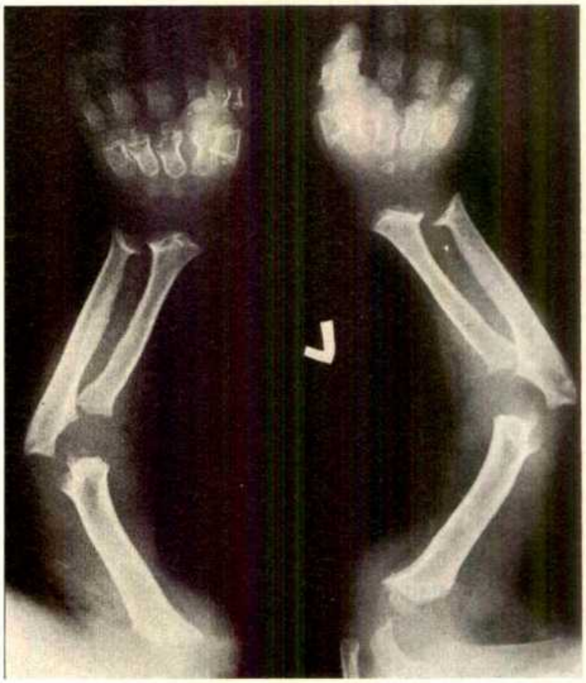

FIG. 11. *Case 4.*
Age eight years. There is shortening of the tubular bones of the arm and hand with distinct rhizomelic predominance. Metaphyseal flaring and delayed epiphyseal development are present.

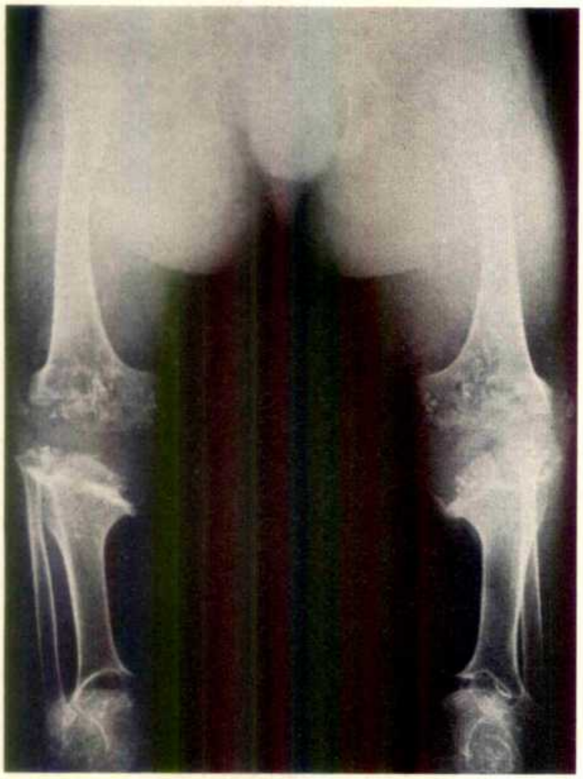

FIG. 12. *Case 4.*

Age 13 years. Shortening of the femora and tibiae with relatively long fibulae with marked metaphyseal flaring and irregularity. The epiphyses are stippled and underdeveloped.

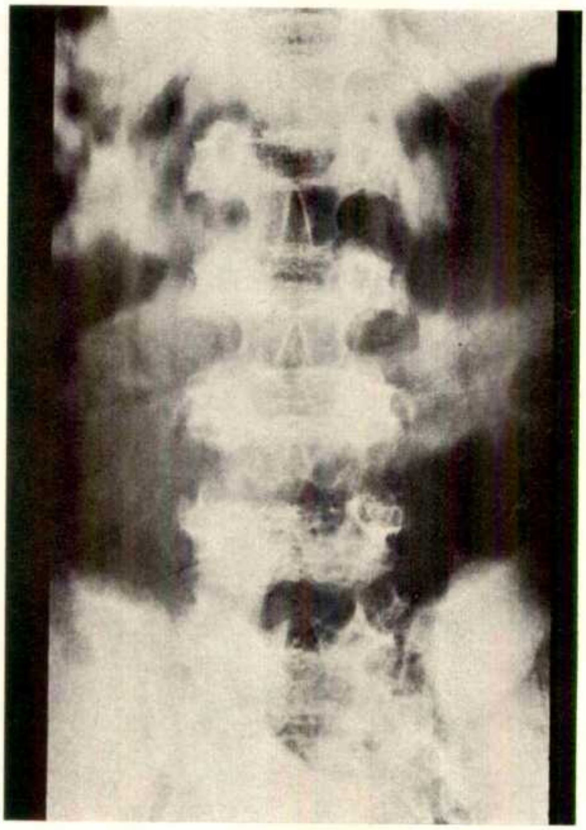

FIG. 13. *Case 5.*

Age eight years. Platyspondyly and widened disc spaces are evident in the lumbar spine.

The acetabula were dysplastic and the proximal femoral epiphyses were small (Fig. 9). Triangular-shaped distal femoral epiphyses fitted into notches in the flared distal femoral metaphyses. The proximal tibial metaphyses were also somewhat expanded.

Kindred 2 (autosomal recessive—severe form)

The proband was a severely dwarfed 18-year-old male, of Cape coloured stock. His younger brother was similarly affected, but the parents and eight other siblings were normal. The parents were consanguineous.

Case 4

T.R., the proband, born in 1956, presented at the age of eight years with genu varum and club foot deformities. At that time, he was thought to be an achondroplast. Corrective surgery for clubbed feet and bow legs was subsequently carried out.

The patient was re-examined in 1972. He was found to be 91.5 cm in height, with an arm span of 76 cm. Limb shortening and a moderate lumbar lordosis were obvious features. His fingers were stubby and the joints of his hands and wrists were lax. Elbow extension was limited.

Radiographically, the skull was normal. Platyspondyly, with marked anterior beaking and increased disc spaces were striking features in the spine (Fig. 10). The pelvis showed dysplastic acetabula, small sacro-iliac notches and underdeveloped pubic rami.

Shortening was a feature of all segments of the tubular bones of the arms (Fig. 11) and legs (Fig. 12). Delayed maturation of the proximal and distal femoral and proximal tibial epiphyses was evident. Marked flaring of the distal femoral and proximal tibial metaphyses was associated with slight genu varum. The tarsal bones were dysmature and malformed and talipes equinovarus deformities were present. The shoulders were subluxated and the glenoid fossae were dysplastic. Delayed development of the epiphyses of the elbow, shoulder and carpal bones was evident. The phalanges were broad and shortened.

Case 5

A.R., the brother of the proband, was born in 1962. Genu varum was noticed in early childhood and at the age of seven years corrective bilateral tibial osteotomies were undertaken.

When examined at the age of ten, he was 91 cm in height, with a span of 84 cm. His physique was similar to that of his affected brother. Proximal shortening of his limbs and a mild lumbar lordosis were present. The digital and wrist joints were hypermobile, while elbow extension was restricted. With the exception of the talipes equinovarus deformities in the feet, the radiographic changes were virtually identical to those of his affected brother (Figs. 13, 14 and 15).

SPORADIC PATIENT

Case 6 (autosomal dominant—severe form?)

R.W., a white female, was born in 1950. Her parents, who were unaffected and non-consanguineous, were both in

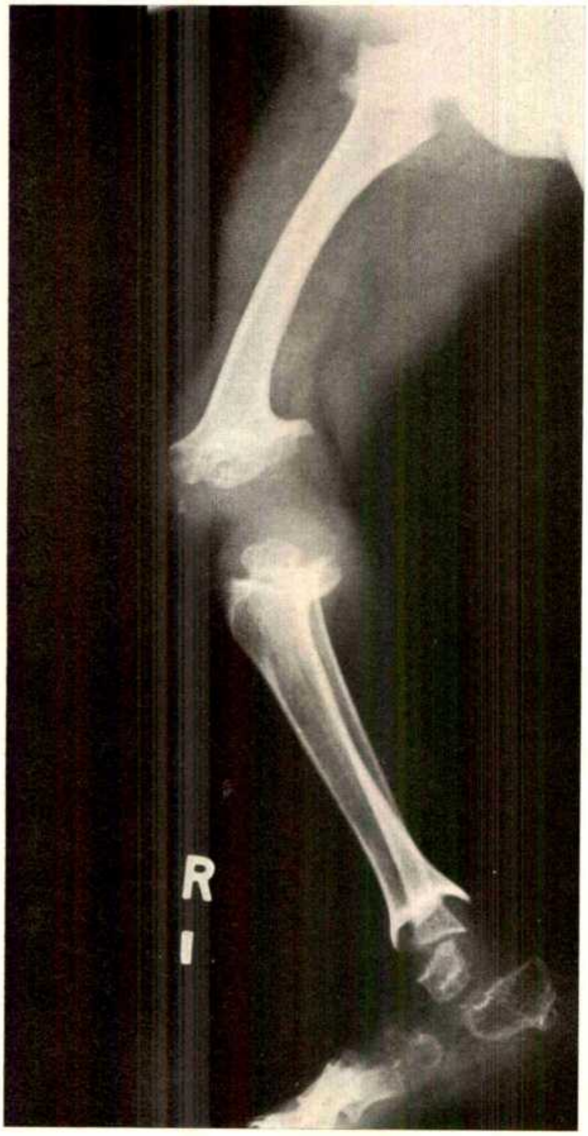

FIG. 14. *Case 5.*
Age eight years. The tubular bones of the leg and foot are shortened with irregular flared metaphyses and maldeveloped epiphyses and tarsal bones.

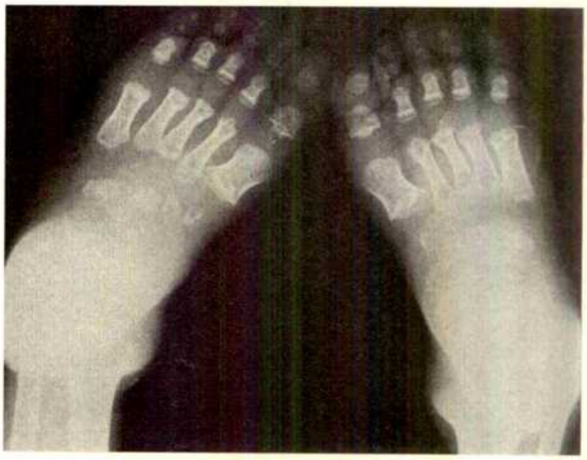

FIG. 15. *Case 5.*
Age eight years. Talipes equinovarus deformities are present with shortened metatarsals and phalanges and irregularly developed tarsal bones.

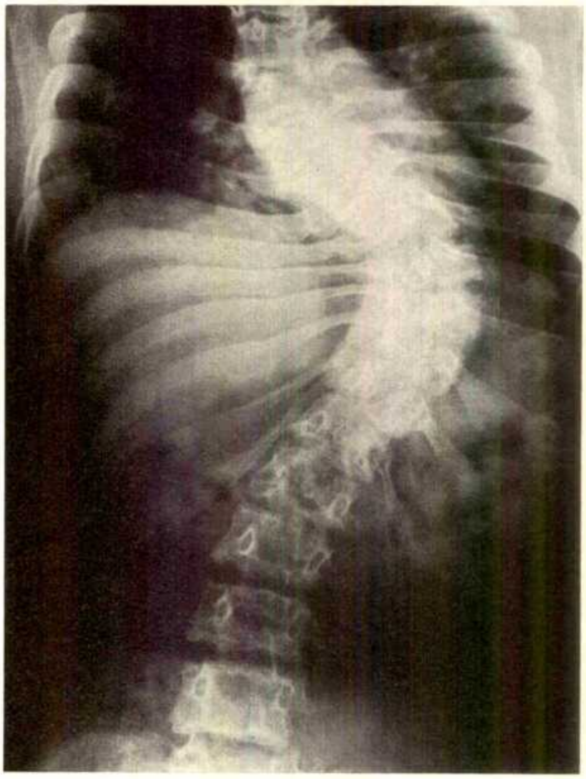

FIG. 16. *Case 6.*
Age 15 years. Marked dorsolumbar scoliosis is present. The ribs are narrowed posteromedially.

their twenties at the time of her birth. Her elder sister and all other members of the kindred were normal.

At the age of two, she suffered two episodes of transient quadriplegia, of undetermined cause. It then became increasingly apparent that her stature was short and thereafter she wore calipers for instability of the knee joints. The right knee was arthrodesed when she was aged 12. A lower dorsal kyphoscoliosis appeared at the age of four and progressed in spite of treatment with plaster casts and braces until she was 16 years of age, when it became stable. Her general health remained good, and in spite of her disabilities, she lived an active life working as a bank clerk. On examination in 1972, the patient was found to be severely dwarfed, with

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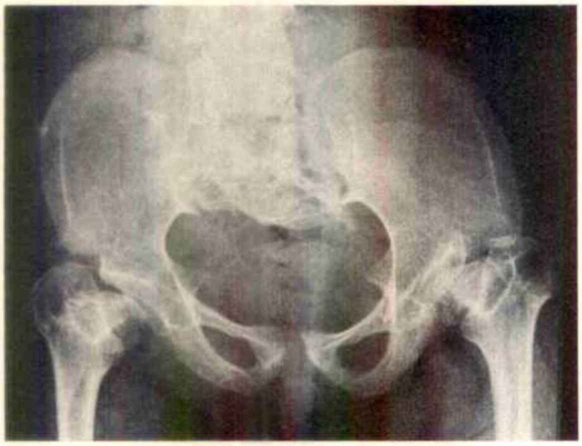

Fig. 17. *Case 6.*
Age 22 years. The sacrum articulates low on the ilia and is sharply angulated posteriorly. The iliac bones show increased flare and dysplastic acetabula. The femoral heads are grossly flattened and malformed.

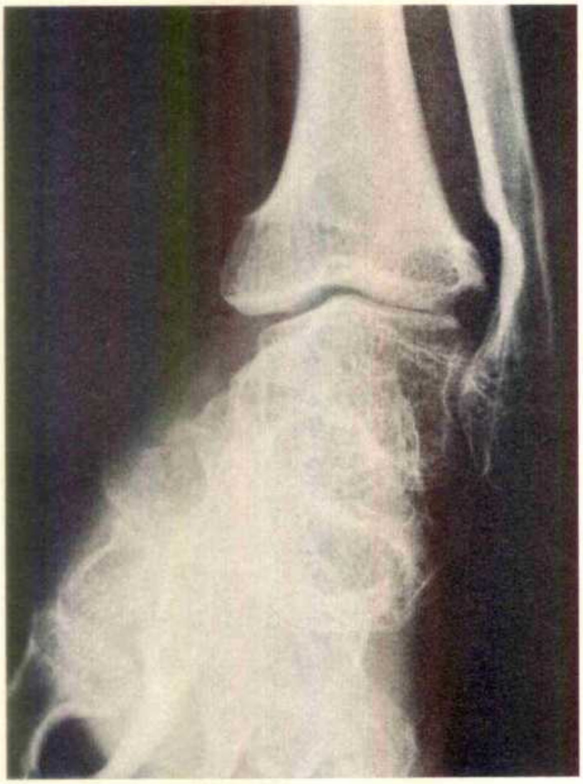

Fig. 18. *Case 6.*
Age 22 years. Relatively long fibula with mis-shapen distal tibiae and maldeveloped tarsal bones are evident.

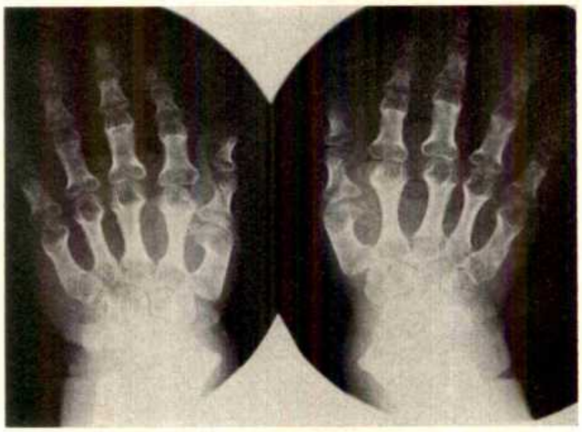

Fig. 19. *Case 6.*
Age 22 years. Short phalanges and metacarpals and a triangular configuration of the carpal bones are present. The malformed distal radius shows marked medial slope. The distal ulna is dislocated, mis-shapen and shortened.

proximal shortening and mild bowing of the limbs. Her height was 108 cm and her span 98 cm. She had marked thoraco-lumbar kyphoscoliosis, with lumbar lordosis, but the configuration of the thorax was normal. The digits were short and stubby, with disproportionate widening of the nails.

With the exception of the elbows, which could not be fully extended, and the right knee, which had been arthrodesed, the joints were very hypermobile.

On palpation, her skin had a soft, doughy quality. There was no neurological evidence of spinal cord compression, and clinical examination was otherwise normal.

On radiographic examination the skull was normal. The spine revealed a gross dorsolumbar scoliosis (Fig. 16). The pelvis showed marked acetabular dysplasia, posteriorly directed sacrum and underdeveloped iliac bones (Fig. 17). The femoral necks and shafts were shortened with flattened underdeveloped femoral heads. Deformity and flaring of the distal femora and proximal tibiae were apparent, with evidence of previous surgery to the right knee and genu valgum deformities. The fibulae were relatively long and the tarsal bones were deformed (Fig. 18).

The tubular bones of the upper and lower limbs were shortened with rhizomelic predominance. The humeral heads were flattened and the glenoid cavities were dysplastic. The distal radius was malformed with marked medial slope and a triangular configuration of the mis-shapen carpal bones was evident. The phalanges and metacarpals were short and stubby (Fig. 19).

Discussion

In their classification, Hall and Dorst (1969) defined four types of pseudoachondroplasia. The eponym of Kozlowski was associated with the mild Types I and II, and that of Maroteaux-Lamy with the severe Types III and IV. According to this classification, Types I and III were inherited as autosomal dominants, while Types II and IV were autosomal recessives (McKusick, 1972). Hall (1975) reviewed the features of 28 cases of pseudoachondroplasia in eight families and discussed these various subgroups. She concluded that the two recessive forms could be distinguished on the basis of their radiological changes. However, she was dubious as to the clinical and radiological differentiation of the dominant varieties.

In our series of 13 patients we have been unable to categorize all our cases purely on radiological appearances, without knowledge of the genetic background. However, some positive findings in this regard emerged. Scoliosis and odontoid hypoplasia are reported as being most common in Type III pseudoachondroplasia (Bailey, 1973; Lindstrom, 1974; Hall, 1975). Our only case (Case 6) exhibiting a scoliotic deformity has in fact been classified as Type III pseudoachondroplasia (severe autosomal dominant —mutant) and, indeed, her transient quadriplegia may well have been the consequence of odontoid hypoplasia and limagentous laxity. Type IV pseudoachondroplasia is the most severe form of the disorder (Bailey, 1973). Our most severely affected patients (Cases 4 and 5) have been, with knowledge of their genetic background, categorized as Type IV (severe autosomal recessive).

We have categorized Cases 1, 2 and 3 as mild autosomal dominants (Type I). Cases 7, 8 and 9 could not be confidently assigned to any specific category other than mild or severe. Case 10 probably has the severe, autosomal recessive form (Type IV) and Case 11 the mild, autosomal recessive (Type II). Case 12 and 13 represent the mild, autosomal dominant (Type I).

Notable advances have been made in the elucidation of the basic defect in pseudoachondroplasia. Cooper *et al.* (1973), studied cartilage from affected individuals and demonstrated inclusions in the rough-surfaced endoplasmic reticulum. However, these findings, although apparently specific for pseudoachondroplasia, did not permit recognition of the various types of the disorder.

The bow leg deformities, which are a common feature of pseudoachondroplasia, may lead to a mis-diagnosis of Vitamin D resistant rickets and the metaphyseal irregularities to a mis-diagnosis of metaphyseal chondrodysplasia (metaphyseal dysostosis) (Silverman, 1973).

As pseudoachondroplasia is not clinically or radiographically evident until early childhood, it does not enter into the differential diagnosis of the newborn short limbed dwarfs (Cremin and Beighton, 1974). Pseudoachondroplasia must be differentiated from achondroplasia, spondyloepiphyseal dysplasia and the Morquio syndrome (Mucopolysaccharidosis IV) (Lichtenstein, 1974; Rupprecht and Purath, 1973; Lindseth *et al.*, 1967). Achondroplasia can be recognized by the typical skull, trident hands and vertebral changes which are present at birth. Caudal narrowing of the interpedicular distances in the lumbar spine occurs typically in achondroplasia and is not usually a feature of pseudoachondroplasia (Dorst *et al.*, 1972).

Spondyloephyseal dysplasia congenita differs from pseudoachondroplasia in that it manifests at birth and that epiphyseal and metaphyseal changes are more marked, although shortening of tubular bones is not severe. Involvement of the hands and feet are minimal. Spondyloepiphyseal dysplasia tarda is x-linked and occurs only in males. Failure of normal growth becomes apparent between the ages of five and ten. Heaping up of the superior aspects of the vertebral bodies is a pathognomonic feature. Morquio's disease may be diagnosed by the end of the second year of life. The radiographic stigmata are those of dysostosis multiplex. Keratosulphaturia usually differentiates the conditions.

Pseudoachondroplasia is a much commoner condition than is generally appreciated. Considerable heterogeneity exists and mild and severe types have been delineated, with dominant and recessive forms. Classification, purely on radiological appearances, is not possible in all cases. However, with knowledge of the genetic background, and awareness of the stigmata of the various types of the condition, effective management and genetic counselling is usually possible.

Acknowledgments

We are grateful to Mrs. S. Henderson for her assistance with the illustrations and to Sisters L. Durr, L. Groeneveldt and R. Duggan for co-ordinating the studies.

We thank our colleagues who referred patients to us. In particular Mr. B. Jones, F. Machanik and Professor L. Solomon deserve our gratitude.

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ADDENDUM:

Since this report was submitted, a further publication of eight cases of the severe type has been recorded in *Australasian Radiology*. "Pseudoachondroplastic Dysplasia" (Maroteaux-Lamy), K. Kozlowski, Vol. 20, 255–269, 1976.

Book review

SPIE Vol. 56. Medical X-Ray, Photo-Optical Systems Evaluation. Edited by K. E. Weaver, R. F. Wagner and D. J. Goodenough. Pp. 246, 1975 (California, U.S.A., The Society of Photo-Optical Instrumentation Engineers), $34.00.

This report is the proceedings of a symposium held in October 1974 in Columbia, Maryland and organized by the Bureau of Radiological Health with the aim of identifying universally accepted parameters for specifying the performance of components of medical imaging systems in the belief that image quality might then be optimized and administered radiation dose minimized.

The symposium was organized with sessions on five related topics and the proceedings include copies of the invited papers together with a verbatim report of the following panel discussions. A minimum editing of the recorded discussion has been given with the intention of conveying the atmosphere of interesting exchange. What in fact comes over is the gulf between those asking the basic questions and those giving the answers. For example, to the question "What is the minimum amount of pathology seen with a good imaging system for cerebral angiography?" is given the answer, "There is really no way you can increase system speed without paying some price for it." This was well summed up in the introductory lecture to one of the sessions by the late Dr. Kurt Rossmann—"We should be asking, what special purpose systems can be designed to offer increased diagnostic certainty? and How much can patient exposure be reduced without a decrease in diagnostic certainty?, but at the moment we can only make measurements of modulation transfer function, Wiener Spectrum and other similar physical parameters".

The first session on film-screen sensitometry discussed the new American National Standards Institute (A.N.S.I.) definitions of speed and contrast, and gave proposals for quality control programmes similar to those discussed at the recent Hospital Physicists Association meeting on quality control. The second session on film/screen optics started with the now standard discussion of resolution and noise, moved through the perceptibility curve and ended with the receiver-operating characteristics curve. The problem was then clearly stated by Dr. D. J. Goodenough—"We must keep in mind that we are not dealing with just a physical system but also the interaction between the system and the doctor. We must keep in mind the extremely high error rate inter- and intra-observers." He concluded that both physical and psychophysical measurements of system performance are needed in order to quantify relative improvements in diagnosis resulting from changes in physical parameters, quality control and training of radiologists. At the moment the ROC approach would seem to be the best method for examining overall system performance.

The third session pursued the testing of image-intensifier systems without reaching any useful conclusions other than identifying the need for a simple test object for quality control purposes. The fourth session on focal spots discussed the problems of checking the manufacturer's specification, particularly with microfocus tubes, and of Gaussian intensity distributions, but without being able to correlate focal spot properties with imaging performance. Finally, the fifth session looked at new developments such as xeroradiography, ionography and computer tomography.

Overall the symposium failed in its objective, which is hardly surprising since discussions on radiographic image quality have been going on for many years without any apparent signs of progress. Nevertheless the proceedings are a useful summary of the present situation (even though two more years have now elapsed) and would be particularly helpful to newcomers to the field.

M. DAVISON.

1977, *British Journal of Radiology*, *50*, 483–488 JULY 1977

The use of abdominal contrast tomography in liver disease

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(*Received June, 1976 and in revised form October, 1976*)

ABSTRACT

The value of a high dose infusion technique using urographic contrast medium followed by tomography was studied in 44 patients with liver disease. The method was found to be of value in showing cysts, abscesses and cystic disease of the liver. Large tumours, primary and secondary, can also be demonstrated. Normal bile ducts are not visible, but become apparent when they are dilated.

The term "abdominal contrast tomography" has been used earlier (Dalla Palma and Moretti, 1974) to refer to a technique for tomography of abdominal structures opacified by the rapid infusion of contrast medium. The technique is based on the so called "total body opacification" first described by O'Connor and Neuhauser (1963) in three children undergoing urography. Subsequent papers from the same department (Griscom, 1965; Griscom and Neuhauser, 1966; Martin *et al.*, 1972) showed the usefulness of total-body opacification in childhood, particularly in neonatal masses. At first it was thought that the technique was not applicable in adults but Kittredge *et al.* (1966) showed the possibility of opacifying abdominal masses in adults. Other indications of the value of total body opacification in the adult were given by Morgan and Johnson (1970) in the diagnosis of splenic masses, by Genereux and Tchang (1970) in the diagnosis of obstructive cholecystopathy and by Mitty and Schapira (1972) and Hatfield and Pfister (1973) in the diagnosis of poorly vascularized lesions of liver and spleen.

We have been interested in the use of tomography during total body opacification for some years, both for general use in the abdomen (Dalla Palma and Moretti, 1974; Dalla Palma 1975), and in the diagnosis of pelvic masses (Dalla Palma *et al.*, 1976). We now wish to present the results obtained in liver opacification.

MATERIAL AND METHODS

We have studied 44 patients. Twenty-five had liver enlargement or hepatic masses, three had hydatid liver disease, 14 had ascites due to various causes (cirrhosis, ovarian tumour etc.) and two had obstructive jaundice. In addition, in 145 subjects with kidney disease, the liver was included in the examination so as to define the normal appearances.

The technique is based on the rapid infusion of 150 ml of 66·8% sodium iothalamate (Conray 400), equivalent to 60 g of iodine. The contrast is diluted with the same volume of 5% Dextrose.

In all cases we have used linear tomography with a 40 deg. angle of swing; the tomography is undertaken at the end of the infusion. The layers are 1 cm apart, from 6 to 16 cm above the table when the liver is of normal size and up to 20 cm or more when it is enlarged. We often consider a second series of tomograms when the diagnostic problem has not been resolved by the first series.

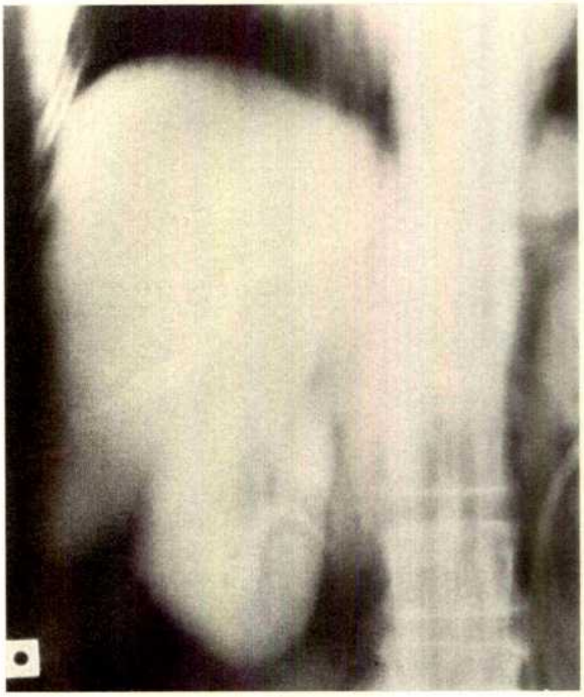

FIG. 1.

Normal liver with medium development.

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It is useful to begin the examination with a few tomograms of the hepatic area, in order to determine the quality of the exposure and correctness of the centering. Good beam collimation is necessary to give the best quality and detail. Correct exposure values are very important; the beam must be sufficiently penetrating to demonstrate lucent areas which are not apparent when the film is under-exposed or over-exposed.

No patient has complained of symptoms due to the rapid infusion.

RESULTS

In all our cases we have obtained intense opacification of the liver, dense enough to allow the evaluation not only of its margins but also its homogeneity in all the tomograms. Hepatography is very intense in the first few minutes following infusion and lasts sufficiently well to allow interpretation for about 10 min., during which all the tomograms necessary for diagnosis must be obtained.

The shape of the normal liver varies, with predominantly medium, horizontal or vertical development (Figs. 1 and 2): these variations have been well described by Lamarque (1974). In the "medium" liver, length is approximately equal to width (±4 cm). In the vertical liver, length is over 4 cm more than width: in the horizontal liver, width is over 4 cm more than length. The medium and vertical livers are easily evaluated. The study of the left portion of a horizontal liver may be impaired by the underlying vertebrae but even so lucent areas in this region may be seen.

The opacification of the normal liver is homogeneous, except for a few cases showing lucent areas along the outer right border which we believe are due to rib indentations. In most cases the hilum may be visualized as a faint lucency surrounding the portal vein: the latter may be seen as far as its bifurcation into right and left branches; more proximally the distal part of superior mesenteric and splenic veins may be shown. Sometimes the calibre

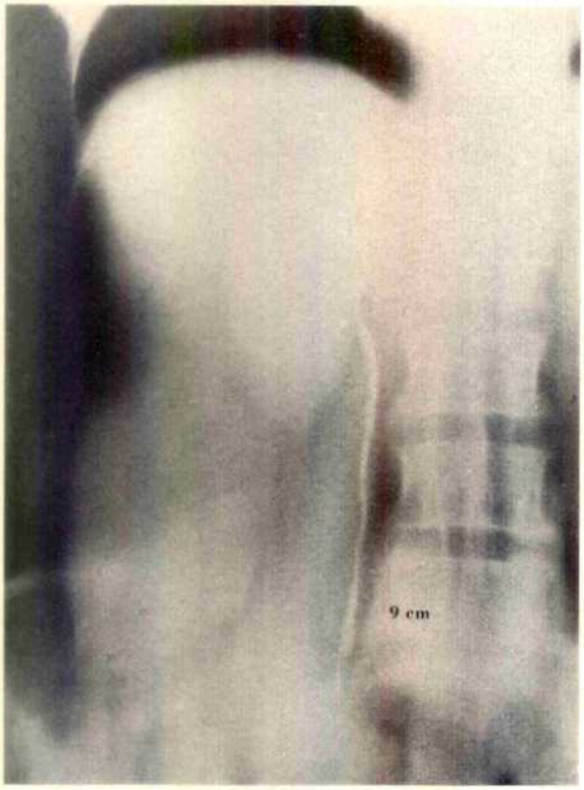

FIG. 2.
Normal liver with vertical development.

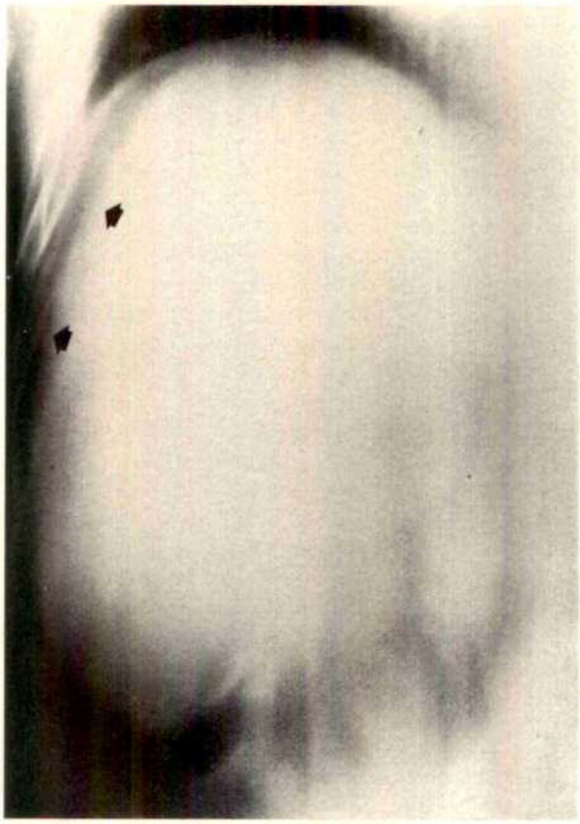

FIG. 3.
Cirrhotic enlarged liver displaced from the abdominal wall by ascites. The arrows show the irregular border.

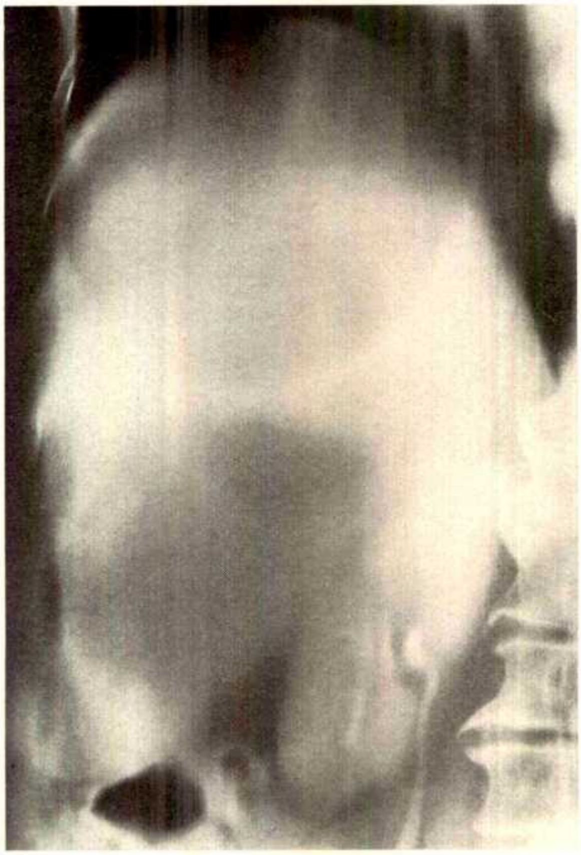

FIG. 4.

Echinococcus cyst: three large areas of lucency may be seen; on this tomogram the superior one is in focus and shows a uniformly thick wall.

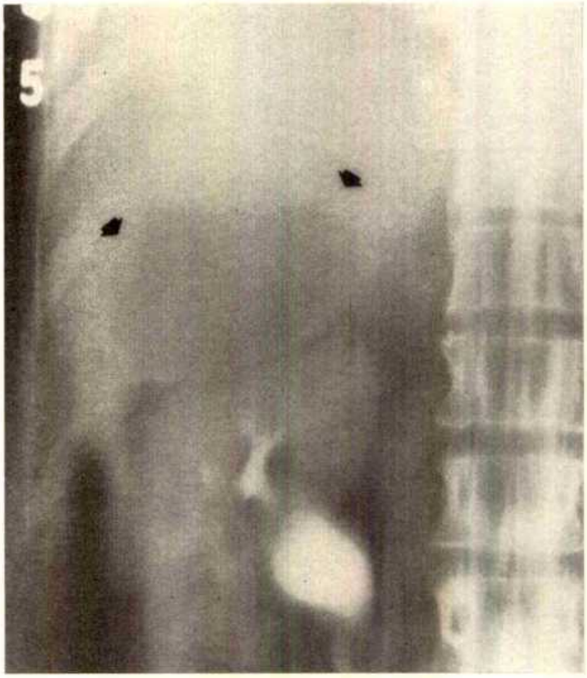

FIG. 5.

The lower border of the liver shows an oval lucent area, with a thick wall: abscess in a diabetic patient.

and course of these veins may be demonstrable but less often than the portal vein which is not disturbed by other superimposed images.

Anomalies of the liver such as hypertrophy or atrophy of one or more segments are well demonstrated when they deform the liver outline. When the right margin of the liver is displaced from the lateral abdominal wall it is possible to diagnose ascites (Fig. 3). The displacement is proportional to the amount of peritoneal fluid and the presence of fluid allows the demonstration of quite minor irregularities of the liver margin, for example in cirrhosis. The severity of the disease may be estimated by the degree of liver deformity and shrinkage.

The technique is particularly valuable in the diagnosis of space occupying lesions with a poor blood supply. These show as areas of lucency, varying according to the nature of the process. The lucent areas found in cysts are homogeneous. In parasitic cysts the border is sharp with a regular wall surrounding a sometimes enormous space (Fig. 4). In one of our cases the inferior outline of the cysts lying along the lower border of the liver was not visualized because the cyst was not surrounded by liver parenchyma.

In polycystic liver the lucencies may be so numerous as to replace most of the organ. The liver is then faintly opacified and the pattern is not as striking as in hydatid disease; the cyst margins are less well defined, probably because there are so many that the margins are irregular.

The ability to visualize these lucencies is an indication for the technique in all patients with polycystic kidney, in order to see if the process also involves the liver.

Lucent areas due to abscesses are also well demonstrated. We have seen one in a diabetic patient (Fig. 5). Lucent areas are seen not only in cystic and cavitating processes but also in solid ones particularly in primary or secondary neoplasm with a poor blood supply, whether throughout the lesion or only in some areas; the lucent areas coincide with necrosis in the tumour. Metastases were visualized as homogeneous lucent areas with a sharp smooth

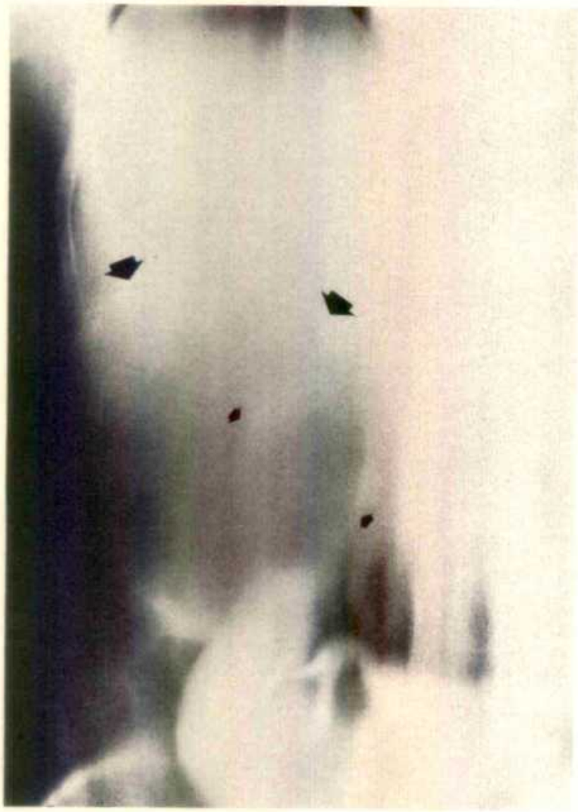

Fig. 6.

Gall-bladder cancer widely invading the liver. Large lucent area occupying most of the right liver: it has irregular blurred margins superiorly (large arrows). The small arrows show the gall-bladder's thickened wall.

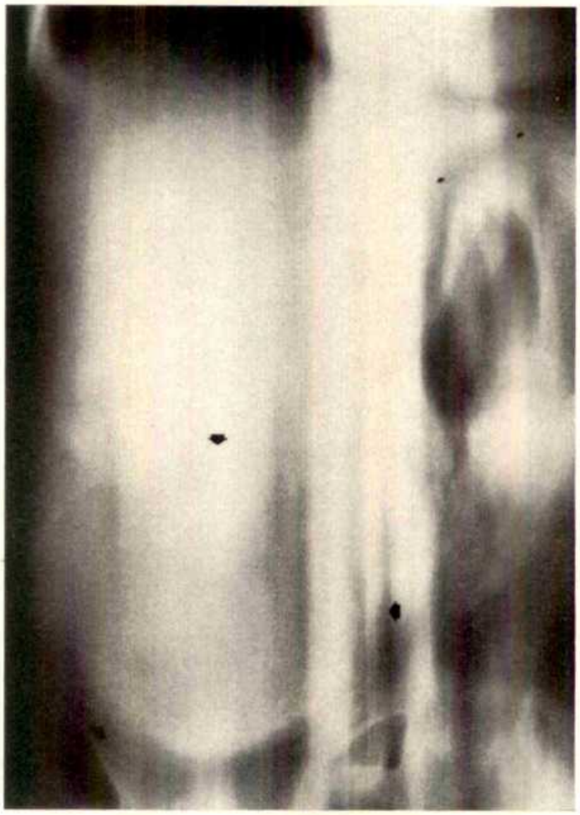

Fig. 7.

Large metastasis of an anaplastic cancer of unidentified origin. A round non-homogeneous lucent area with a thick wall may be seen.

margin if the lesion was capsulated and with an irregular, sometimes blurred outline if the lesion was infiltrating (Figs. 6 and 7).

In two patients with large metastases and in one with a hepatoma we noted opacification within the mass; in the case of the hepatoma this was not homogeneous (Fig. 8) perhaps because of the presence of necrosis. If a tumour is completely opaque it does not become visible because it cannot be separated from the normal opaque parenchyma; one may sometimes suspect the presence of a lesion when it lies on the liver margin producing a bulge (Fig. 9). Arteriography is important in such cases because it may help in the differential diagnosis of a malignant growth from deformity due to hypertrophic segments.

Finally, we should mention the demonstration of the biliary tract. The dilatation of bile ducts may be shown as lucencies which produce a negative image of the biliary tract or "negative cholangiogram" (Fig. 10). We would stress that the biliary tract is not seen if its calibre is normal. These data will be considered in more detail in another report on the contribution of abdominal contrast tomography in the evaluation of the biliary tract.

Discussion

In this preliminary report we have shown that a water soluble contrast medium injected in sufficient quantity and short enough time to produce a high plasma concentration will result in a good parenchymal opacification lasting 10 to 15 min. The intensity of opacification and its duration are enough to allow a tomographic study of the liver; not only may anomalies of shape and size be studied but also processes which change the homogeneity of parenchymal opacification.

Radiographic hepatography has long been attempted but the problems of finding a suitable contrast have delayed its use in medicine. Thorium dioxide

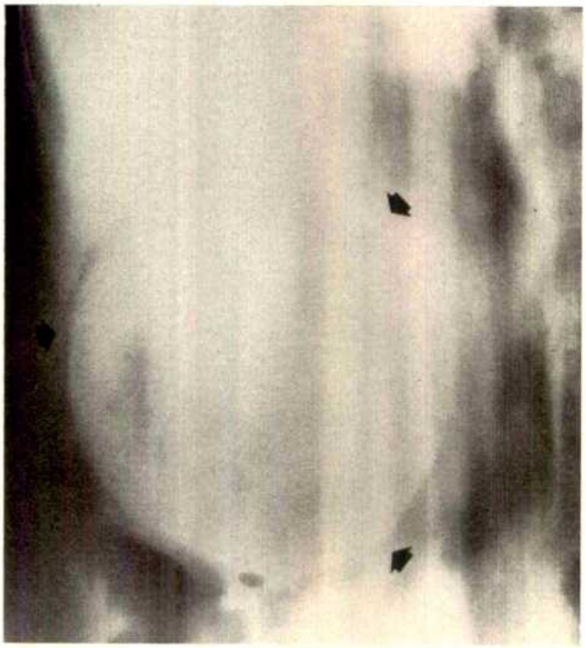

FIG. 8.

Hepatoma: round opaque mass bulging from the liver's lower border: it may be distinguished from parenchymal opacification because of its capsule.

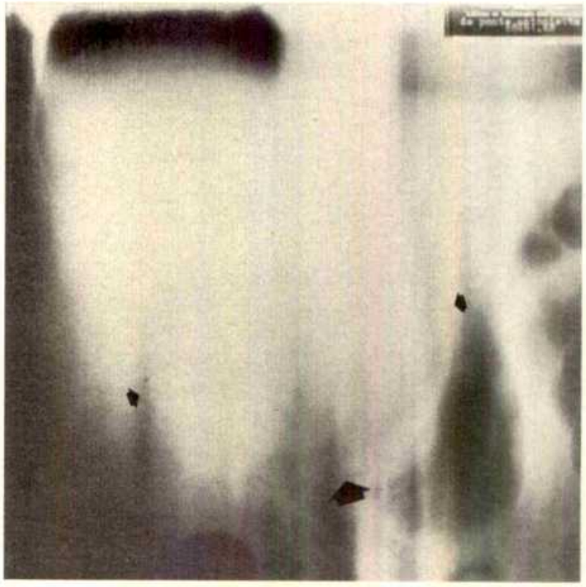

FIG. 9.

Large metastasis from cancer of the pancreas: it is an opaque mass that deforms the liver's lower border.

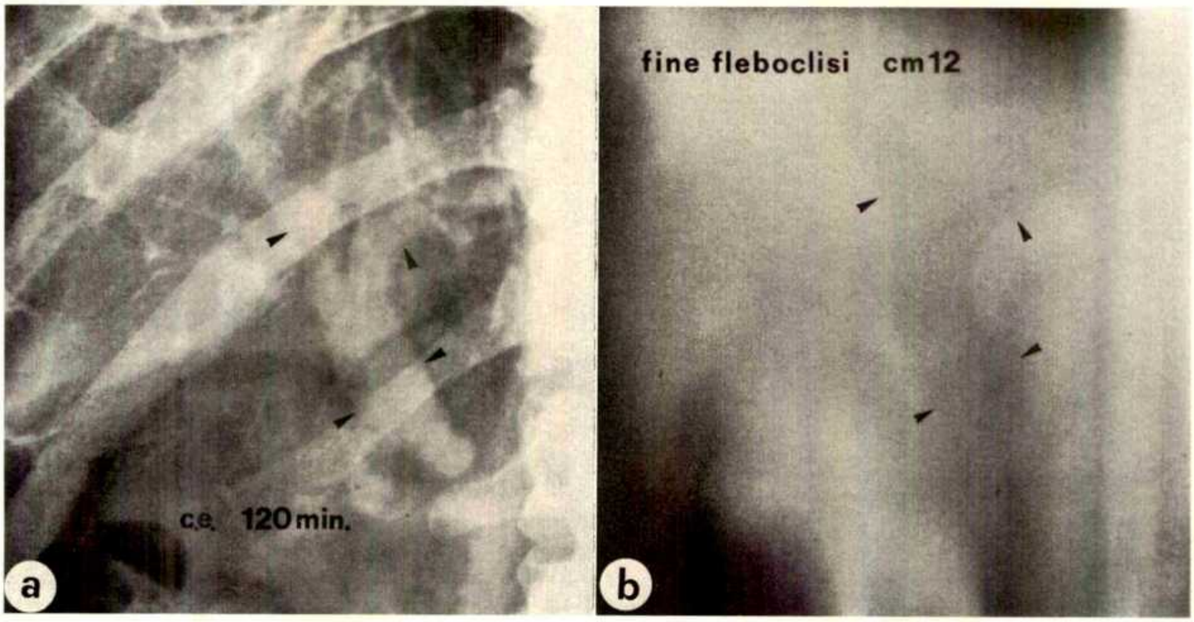

FIG. 10.

Case of cancer of the head of the pancreas and obstructive jaundice.

(A) I.V. cholangiography: the common bile duct is obstructed in its mid-portion and the biliary tract is dilated.

(B) Hepatography a few months later: the lucent area representing the dilated biliary ducts may be seen (negative cholangiogram).

is unsuitable because of the risk of radio-activity. Good opacification of the liver can be obtained with iodinated esters of fatty acids in colloidal suspension and with oily iodinated emulsions (Laval Jeantet *et al.*, 1976; Pinet *et al.*, 1976) but the contrast media are not completely safe, causing reactions in 50% of patients and being contra-indicated in patients with cirrhosis, hepatic failure and problems of blood coagulation. Further experience will be needed to show whether a completely safe contrast medium of this type can be developed. On the other hand hepatography with water soluble contrast medium has proved completely safe. In this preliminary report we have concentrated on the demonstration of gross lesions – those found more easily in routine work – and this simple technique is recommended as a preliminary examination which may be definitive in neoplastic liver enlargement and in the assessment of obstructive jaundice. It may also be of considerable value in cystic diseases and abscesses. Further experience will be needed to show if there are other indications and to assess the reliability of the technique.

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Book review

A Handbook of Paediatric Radiography. First edition by Catherine Gyll, pp. 162, illus., 1977 (Blackwell Scientific Publications), £3·75.

This excellent little handbook, which has been neatly produced in soft covers, does not aim to be a complete textbook of paediatric radiography. Its stated intention is to make available to radiographers in general hospitals some ideas on how to achieve good radiographs of children. Emphasis has been placed upon the need for a satisfactory examination at first attempt and the book is filled with invaluble hints on how this may be achieved.

There are 13 chapters of which the first is a general account of the differences between paediatric and adult radiography and reviews the indications for examination, the different anatomical proportions, problems of exposure factors and radiation protection, methods of immobilization and the need for co-operation from both patient and parent. There follow eight chapters on regional radiography with further chapters concerning the urinary tract, the gastro-intestinal tract, the neonate and a final chapter on special investigations, which includes skeletal surveys, nasal pharyngography, orthodontics and problems on hydrocephalus. More specialized investigations have been excluded on the grounds that these are usually undertaken in specialized paediatric radiological units.

The whole volume is well written, very easy to read and includes many valuble simple line diagrams. Each chapter contains a brief account of diseases unique to the paediatric age group but not all include an indication of the modifications to radiographic technique which these demand. There is little to criticize in this book. Unfortunately, space was not found for a discussion of the problem of prior parental consent. The suggestion that house surgeons should inject contrast medium for excretion urography will be regretted by many readers who will think that this should always be done by a radiologist.

The author is to be congratulated on the quality of this book which succeeds entirely in its primary aim. It should be compulsory reading for all student radiographers, should be available in all general departments which may deal occasionally with children and can be recommended for radiologists studying for the first examination of the Fellowship.

Anne Coombes.

1977, *British Journal of Radiology*, *50*, 489–492

The mammographic demonstration of malignant spicules

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(*Received December, 1976*)

ABSTRACT

A specimen of breast tissue containing a carcinoma with multiple spiculations was used as a test object and examined by a range of mammographic techniques. The images were compared with a photograph of the cleared specimen. A quantitative method of evaluating the performance of each technique is described and used to compare these images. Xeroradiography clearly excelled other imaging methods.

The three primary features of a malignant breast tumour are a mass, calcifications and spiculation (Ackerman and Gose, 1972; Fisher *et al.*, 1975). Any one of these characteristic features alone may lead to the diagnosis.

Several studies have claimed that, when compared with film/screen combinations, xeroradiography provides superior visualization of malignant breast calcifications (Ackerman and Gose, 1972; Fisher *et al.*, 1975; Millis *et al.*, 1976; Tonge *et al.*, 1976). Not all malignant tumours contain calcifications and spiculation may be the only mammographic sign of malignancy, particularly in a dense breast where the tumour mass cannot be identified.

The study described here compares four xeroradiographic techniques, two film/screen techniques and one non-screen film technique, in common use, in the detection of malignant spicules.

METHOD

A suitable tumour having many radiating spicules was chosen pre-operatively. Immediately following mastectomy a 1.00 cm thick section was cut through the centre of the tumour and placed in a plastic petri dish with sufficient normal saline to prevent dehydration. The petri dish with the specimen was then placed on 5.00 cm of fat—equivalent polythene and a series of X ray exposures were made. Details of the imaging methods and techniques are shown in Table I. All radiographs were taken within four hours of mastectomy and the specimen was not moved within the petri dish during this time.

The specimen was then cleared slowly in xylol and oil of wintergreen and when the spicules within it were readily visible, a life size transparency was obtained by photographing it onto 35 mm film and transferring that image on to 4 in. × 5 in. colour reversal film.

Each of the selected X ray images was then placed in turn on a horizontally positioned viewing box so that the centre of the tumour was under the tracing point of a pantograph arranged to give a 2:1 magnification. Viewing conditions for each image—a double tungsten light source for the xeroradiographs and masked transillumination for the films—were adjusted to the satisfaction of each of three independent observers. The image was then transferred onto paper via the pantograph. Where

TABLE I

IMAGING METHODS AND TECHNIQUES

Imaging method	Screen	Development	kVp	mAs	FFD (cm)
Medichrome	Cronex	90 sec	28	Iontomat	43
LoDose	Cronex	90 sec	30	25	43
Kodak PE4006	—	90 sec	30	Iontomat	43
Xeroradiography (molybdenum anode)	—	Positive	30	160	43
Xeroradiography (molybdenum anode)	—	Positive	50	32	43
Xeroradiography (tungsten anode)	—	Positive	35	50	80
Xeroradiography (tungsten anode)	—	Positive	50	20	80

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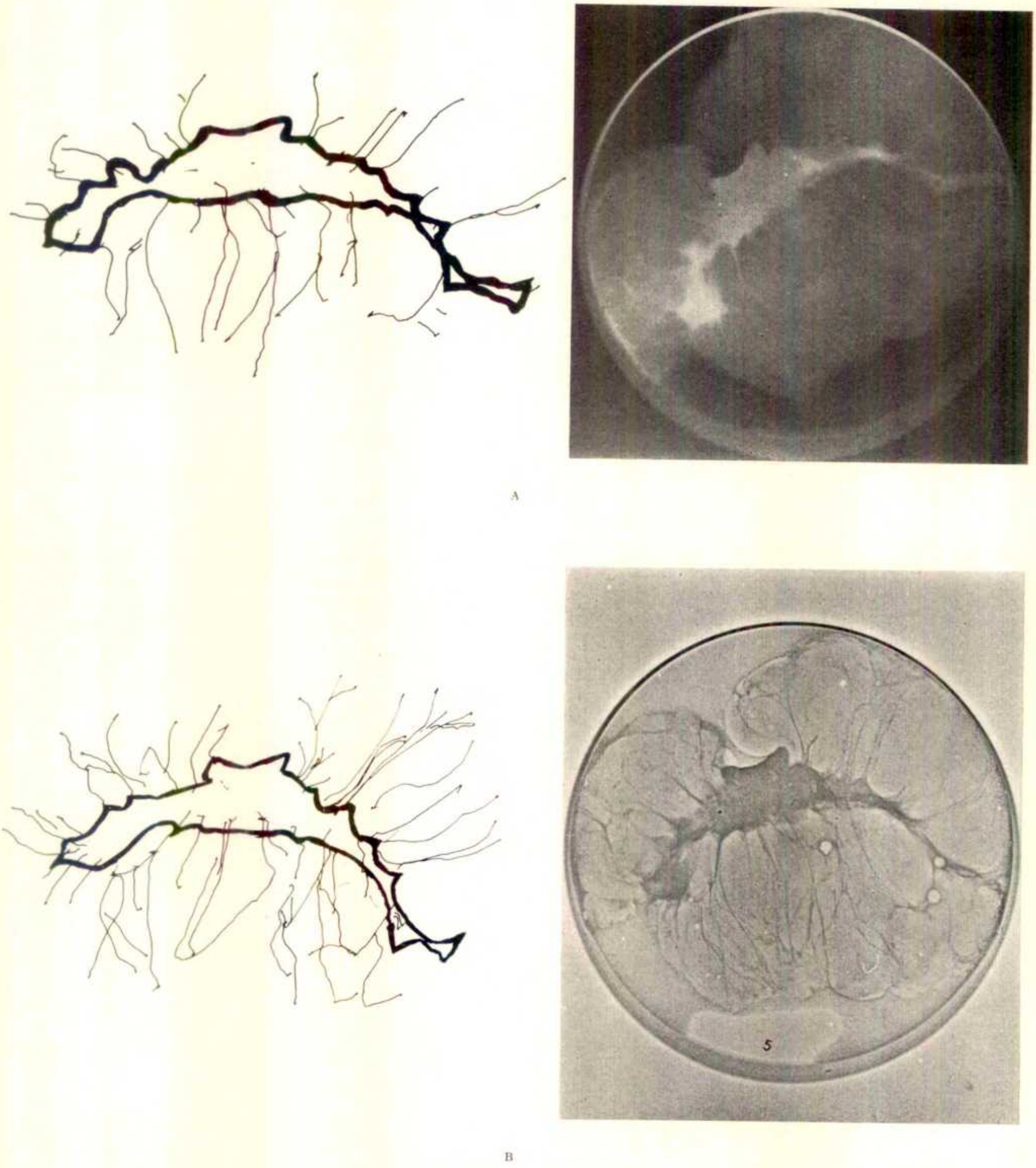

Fig. 1.

Three images and the corresponding pantograph tracings.

(A) Medichrome.

(B) Xeroradiography, molybdenum anode, 30 kVp.

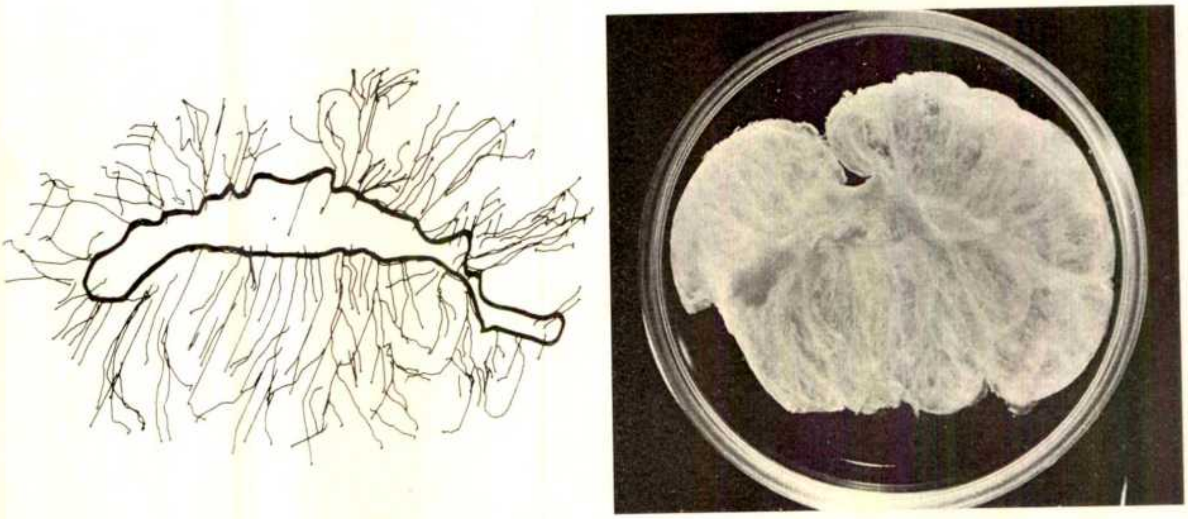

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FIG. 1.

(c) The cleared specimen.

TABLE II

TOTAL NUMBER OF SPICULES COUNTED

Image	Observer A	B	C	Mean
Medichrome	29	34	34	32.3
LoDose	30	30	29	29.7
PE4006	25	24	22	23.7
Xeroradiography (Mo)				
30 kVp	64	61	59	61.3
50 kVp	56	62	50	56.0
Xeroradiography (W)				
35 kVp	63	53	62	59.3
50 kVp	51	51	62	54.7
Cleared specimen				179

lines were present which may or may not have been spicules associated with the carcinoma each observer decided independently which lines to follow and which to leave.

The translucent image of the cleared specimen was then traced in the same way to provide some indication of the total length and number of spicules that could be seen macroscopically. Three representative images and the corresponding tracings are illustrated in Fig. 1.

The line tracings so obtained were measured in two ways. Firstly, the total number of spicules on each tracing was counted. Where the spicule divided each additional branch increased the total count by one. Secondly, the total combined length of all the spicules on each tracing was measured using a map measurer*.

RESULTS

The results are shown in Tables II and III.

DISCUSSION

The importance of using a biological test object for the evaluation of mammographic images was stressed by Tonge *et al.* (1976) in a study of the demonstration of calcifications. In that study it was shown that no imaging method demonstrated all the calcifications present and the study presented here has shown that no imaging method demonstrates even half the number of spicules that can be identified macroscopically.

Measurement of the width of an individual spicule in relation to its radiographic detection presents problems because, unlike calcifications, soft tissue structures are distorted by the fixing process and furthermore spicules tend to decrease in size with increasing distance from the tumour mass. For this reason the total length of spicule and the total number of spicules were selected as indices of performance. Both of these factors are likely to be important when attempting to identify a spiculated carcinoma in a dense breast.

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*W. H. Smith & Co. Limited.

TABLE III

Total length of spicules

Image	Length recorded by each observer (cm) A	B	C	Mean (cm)
Medichrome	41.9	43.8	43.1	42.9
LoDose	45.0	39.4	46.3	43.6
PE4006	36.3	31.3	36.5	34.7
Xeroradiography (Mo)				
30 kVp	98.8	77.5	93.1	89.8
50 kVp	78.8	76.9	81.0	78.9
Xeroradiography (W)				
35 kVp	82.5	67.5	93.3	81.1
50 kVp	76.3	55.0	81.9	71.1
Cleared specimen				180.7

The relatively small difference in performance between the xeroradiographic techniques used here suggests that, for the detection of spicules, the choice of xeroradiographic techniques is less critical than for the detection of calcifications (Tonge *et al.*, 1976). This may be because the difference in attenuation between calcium and soft tissues decreases at a greater rate as the kVp within this range is raised than does the small difference in attenuation between spicules, which are mainly protein, and the surrounding fat (Meredith and Massey, 1972; Spiers, 1946). For the same reason it would appear that the difference in radiation spectra between molybdenum and tungsten targets (Marshall *et al.*, 1975) is of less importance in the detection of spicules than of calcifications. An additional factor may be that linear structures such as spicules may be less liable to be lost in the image noise than rounded microcalcifications (Deichgraber *et al.*, 1974; 1975; Rossman, 1966).

The superior performance of xeroradiography in the detection of malignant spicules suggests that, in a clinical setting, the diagnosis of a proportion of carcinomas will be facilitated if this method is chosen.

Acknowledgment

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Book review

Aseptic necrosis of the bone. Edited by J.K. Davidson, pp.xvi + 336, Illus., 1976 (Excerpta Medica), $60.95.

This is a beautifully produced book on the often mysterious process of aseptic necrosis of bone. It covers the pathology and clinical features as well as radiology. After a long and detailed chapter on pathology by Mary Cattto, there is a section by two surgeons (Graham and Wood) devoted to aseptic necrosis following trauma. The remainder of the book is written by radiologists Jake Davidson on dysbaric osteonecrosis, Bill Park on spontaneous and drug-induced aseptic necrosis, Howard Middlemiss on aseptic necrosis in haemoglobinopathies and Philip Jacobs on the osteochondroses. The radiologists try to present an overview of the subject but quite naturally they provide the greatest detail in the sections devoted to radiology.

Though written for a wider audience this book will clearly be of special interest to radiologists. It is well written, tightly edited and splendidly illustrated. It will remain a standard source of reference for many years to come.

P. Armstrong.

1977, *British Journal of Radiology*, 50, 493–498

Uterine prolapse and urinary tract obstruction

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(*Received January, 1977 and in revised form April, 1977*)

ABSTRACT

Five patients are described with hydronephrosis and hydroureter associated with advanced uterine prolapse. Various hypotheses have been advanced in the literature to account for this neglected syndrome.

A trial was carried out to assess whether all patients presenting with uterine prolapse should be screened to exclude urinary tract obstruction. Thirty-seven patients on the waiting list for surgery for various degrees of prolapse had an IVU and a blood urea estimation. No cases of ureteric obstruction were found, presumably because the lesser grades of prolapse predominated. It is, therefore, considered that all patients with prolapse do not need intravenous urography, which should be restricted to women with complete procidentia.

Dilatation of the upper urinary tract as a complication of uterine prolapse was first described by Froriep (1824). It was again reported by Halban and Tandler (1907) and since then many publications describing the syndrome have appeared (Aboulker, 1938; Danforth, 1938; Fontaine *et al.*, 1962; Wallingford, 1939; Lauras, 1958; Patoir et Spy, 1962; Hébert, 1964; Mueller-Heubach, 1969; Jeukenne, 1970; Schulman, 1970). However most standard English-language texts in radiology and gynaecology still do not describe this syndrome.

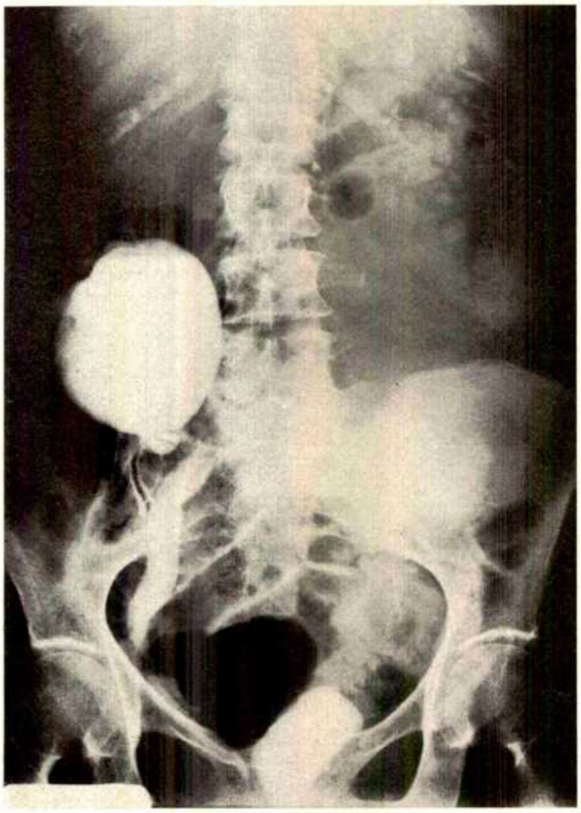

FIG. 1. *Case 1.*

IVU on March 22, 1973 showing gross bilateral hydronephrosis. Concentration on the left is very poor but the distended extra-renal pelvis can be seen occupying most of the left side of the abdomen. The bladder and lower right ureter can be seen descending into the prolapse.

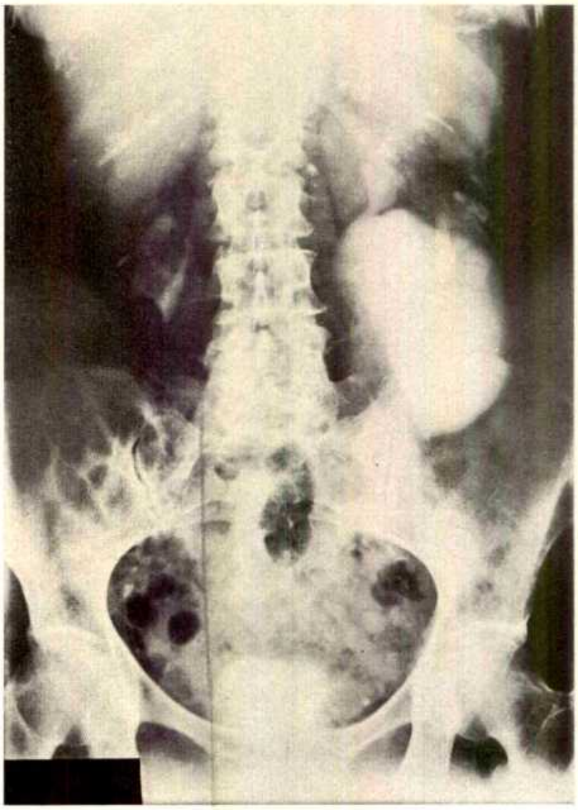

FIG. 2. *Case 1.*

Repeat IVU on April 4, 1973 after treatment of the prolapse with a pessary showing marked reduction of the hydronephrosis on both sides.

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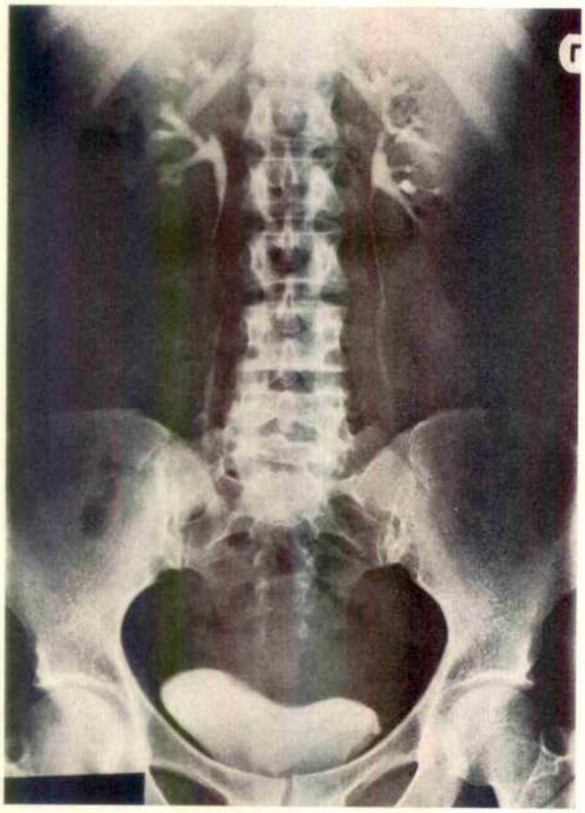

Fig. 3. *Case 2.*
Normal IVU in July 1972.

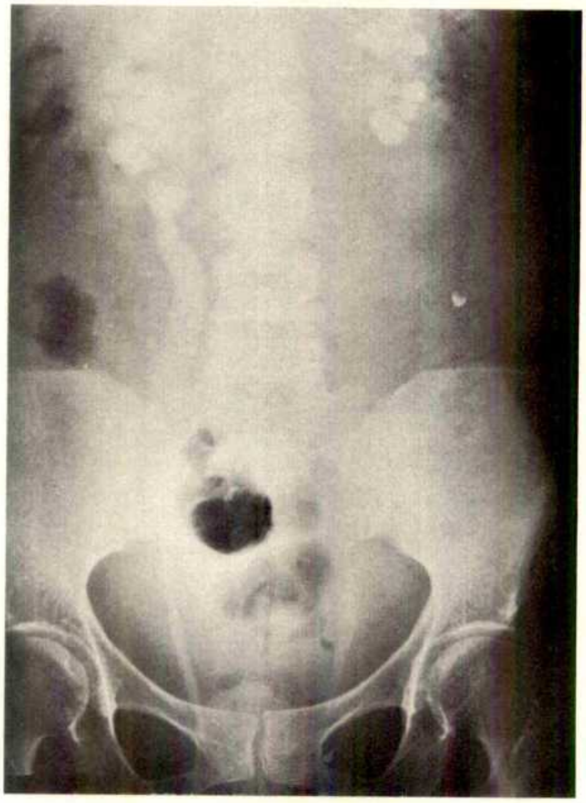

Fig. 4. *Case 2.*
Repeat IVU after development of the ascites and procidentia in February 1974. Bilateral hydronephrosis and hydroureter with descent of the bladder and lower ureters.

Case Reports

The following five cases were encountered within a period of 16 months.

Case 1

A 76-year-old woman was admitted with peri-umbilical and left back pain and a four-day history of vomiting. She was dehydrated and a large tender mass was found in the left subcostal region. She also had a procidentia. An IVU two days later showed an enormous left hydronephrosis, the right ureter descending well below the normal position (Fig. 1). A diagnosis of bilateral hydronephrosis secondary to procidentia was made. The blood urea (BU) was 16 mmol/l. *E. coli* and numerous pus cells were found in the urine.

She was treated with IV fluid, nitrofurantoin and a pessary. The BU fell to 6 mmol/l and a repeat IVU two weeks later showed a striking reduction in the bilateral hydronephrosis (Fig. 2). She was re-admitted after another 11 weeks with a history of further recent attacks of pain in the left flank. Although no mass was now palpable, a repeat IVU showed recurrence of the gross hydronephrosis and *E. coli* were again grown from the urine. She again responded to conservative treatment.

Case 2

A 41-year-old woman suffered from polycythaemia rubra vera. She had a mesenteric vein thrombosis necessitating resection of most of her small bowel, and then developed renal tubular necrosis which responded to dialysis. A follow-up IVU was normal (Fig. 3). Her Hb was 18.7 g% with a haematocrit of 58% and she was treated by venesection. Mild ascites was noted at this time which increased considerably 18 months later. Inferior vena cavography showed hepatic vein occlusion and also bilateral hydronephrosis, which had not been present on the previous IVU. Splenic venography suggested splenic vein thrombosis. It was only at this stage that she was found to have a complete procidentia and she said that she first noted some uterine descent five months earlier. The BU was 10 mmol/l and an IVU (Fig. 4) confirmed bilateral hydronephrosis and hydroureter with descent of the uretero-vesical junctions. Six months later she died following a cerebro-vascular accident.

Case 3

A 71-year-old woman was admitted to a medical ward with crescendo angina and a small myocardial infarct. She also complained of dysuria. The BU was 9 mmol/l. The initial MSU was sterile but haemolytic streptococci were grown from subsequent specimens. An IVU showed bilateral hydronephrosis and hydroureter with the ureters running very low down (Fig. 5). A prolapse was confirmed clinically and she admitted having had it for 13 years. She was discharged and referred for a gynaecological opinion.

On admission to the gynaecological ward two months later, she had a complete procidentia. The BU was 6 mmol/l. She had a vaginal hysterectomy and posterior colpoperineorrhaphy. A follow-up IVU showed resolution of the urinary obstructive changes (Fig. 6).

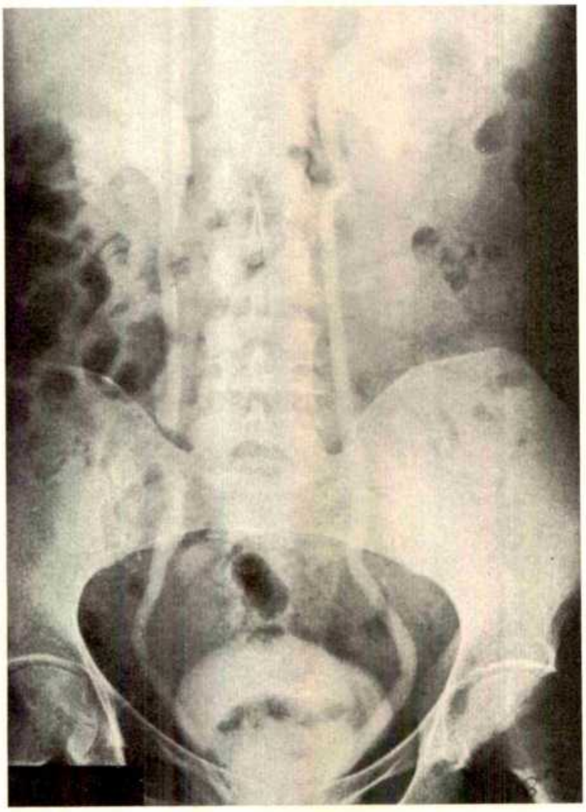

FIG. 5. *Case 3.*
IVU on October 23, 1973.

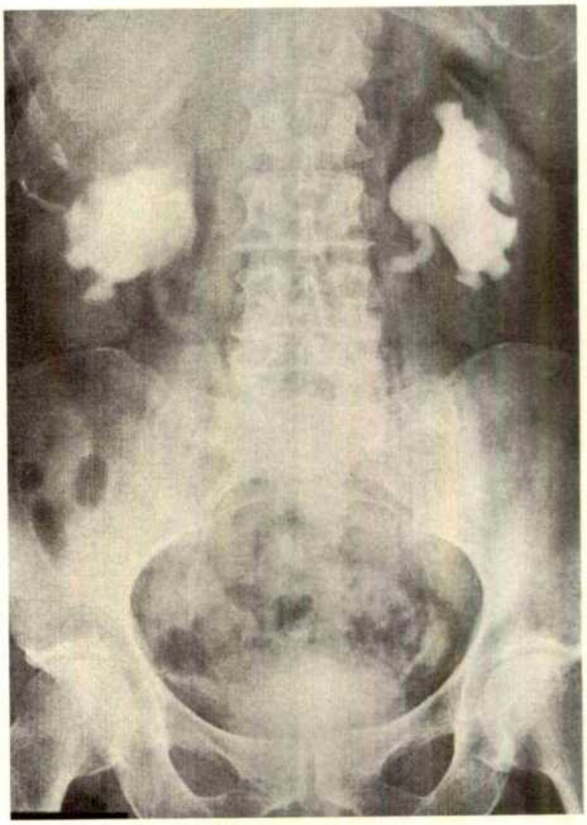

FIG. 6. *Case 3.*
IVU on April 30, 1974. There is marked improvement in the bilateral hydronephrosis after surgical treatment of the procidentia.

Case 4

A 76-year-old woman was found at home by the police in a cachectic state, not having eaten for nine days, and was admitted to a medical ward. She had a large ulcerating procidentia the size of two fists. When able to give a history she said that she had had the prolapse for many years and had to push it back before she could micturate. Her BU on admission was 36 mmol/l. Her urine grew *K. aerogenes*, *Staph. aureus* and *E. coli* on different occasions. When she was re-hydrated, fed and put on antibiotics her BU fell to 11 mmol/l. An IVU (Fig. 7) showed gross bilateral hydronephrosis and hydroureter with thinning of the renal substance. The left ureter was seen to descend into the prolapse. There were large filling defects in the right pelvicalyceal system suggesting matrix calculi.

Although she improved on conservative management, her general condition was still too poor for operation until eventually, ten weeks after admission, she had a vaginal hysterectomy and posterior colporrhaphy. Following this her BU gradually rose again and she died six weeks later.

Case 5

A woman was referred to Gynaecological Out-patients, aged 66, because of uterine prolapse. She gave a history that she had first noticed it 25 years previously and had had a complete procidentia for two weeks. On examination a complete procidentia was confirmed. It was ulcerated and she was admitted for pre-operative assessment and vaginal packing.

On admission however, she presented numerous complex problems. She was in hospital for the next three months and during this time was found to have systemic lupus erythematosus, either idiopathic or drug-induced, with hypoproteinaemia, ascites, defective liver function, thrombocytopenia and various skin manifestations. She developed septicaemia, both *K. aerogenes* and *E. coli* being isolated from her blood. This responded to ampicillin. She also had hypertension (BP 180/110), oral candidiasis, vitiligo, a large para-oesophageal hernia and diverticular disease of the colon.

In view of her procidentia and a blood urea level varying between 10 and 28 mmol/l an IVU was requested. This showed marked descent of the lower ureters into the prolapse and bilateral ureteric obstruction with hydronephrosis (Fig. 8). Her only MSU culture was negative.

Her numerous medical problems and the persistent ulceration of her procidentia precluded operation. She was discharged to the care of relatives in another part of the country and was lost to follow-up.

HYPOTHESES

Various hypotheses have been advanced to explain the association of hydronephrosis and prolapse.

1. Froriep (1824) attributed the stasis to kinking of the urethra. This hypothesis, supported by Stoeckli and Hochuli (1959), has been rejected by most writers since these patients do not have

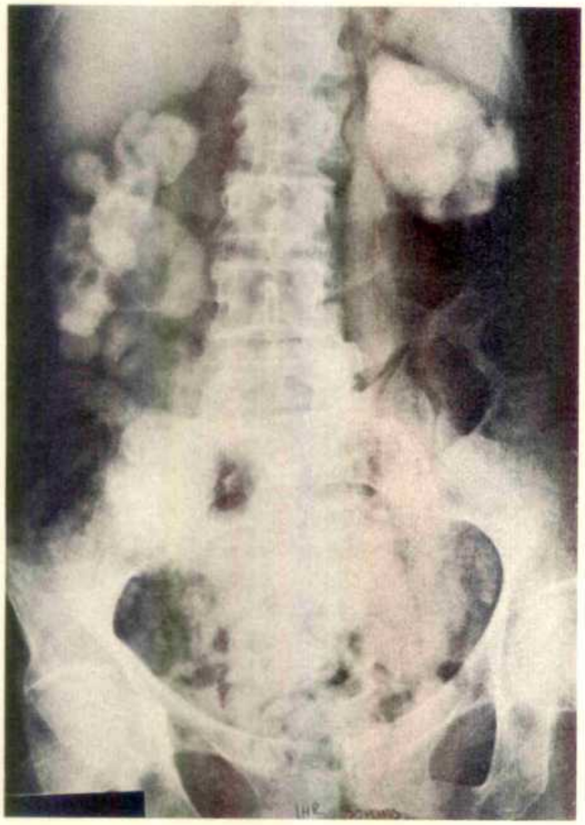

FIG. 7. *Case 4.*

IVU showing marked bilateral hydronephrosis and poor concentration. There are filling defects in the right pelvicalyceal system suggesting matrix calculi. The left ureter is just visible running into the prolapse.

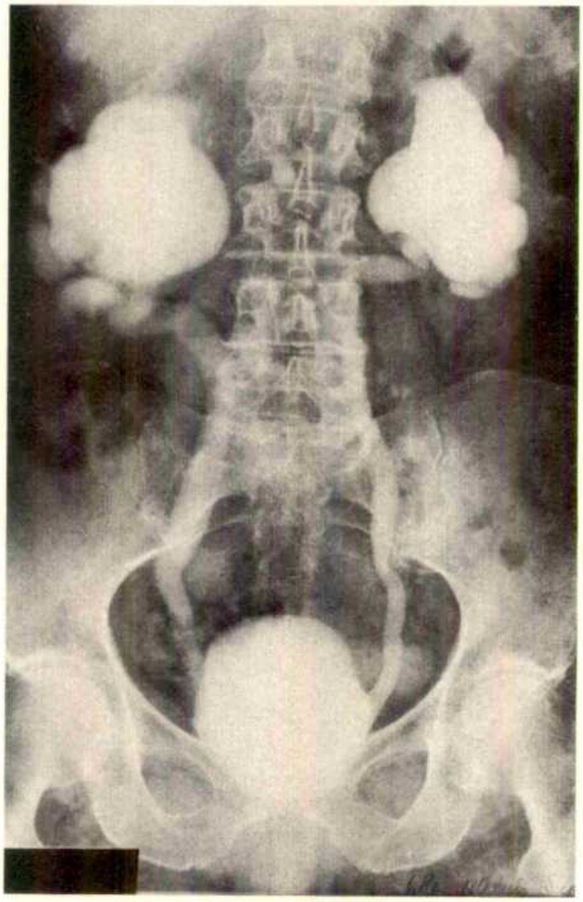

FIG. 8. *Case 5.*

Bilateral dilatation of the upper urinary tract with descent of the lower ureters.

distended bladders and incontinence is the rule rather than retention.

2. Halban and Tandler (1907) attributed the hydronephrosis to compression of the lower ureters between the bladder and the margins of the hiatus genitalis, *i.e.* the levator muscles. Others reject this hypothesis on the grounds that compression of the ureters would only be intermittent, depending on the fullness of the bladder.

3. The hypothesis which has gained widest acceptance is that of Brettauer and Rubin (1923) who attributed the ureteric obstruction to compression by the uterine artery which lies in the broad ligament anterior to the ureter. The hypothesis is that descent of the uterus draws the uterine artery down, compressing the ureter near its lower end.

4. Elkin *et al.* (1974) demonstrated on angiography in one case that the dilatation of the ureter extended 4–5 cm below the level of the crossing of the uterine artery, invalidating Brettauer and Rubin's hypothesis. They suggest that stasis is due to inferior displacement of the trigone causing mechanical deformity and narrowing of the ureteric orifices. This has the virtue of simplicity and seems to the author the best hypothesis advanced so far.

THE PROBLEM

The five cases described above all had a complete procidentia. Did they develop mild ureteric obstruction before they reached this stage or is it necessary to have complete uterine descent before dilatation of the upper urinary tract develops? If obstruction develops in the milder degrees of prolapse as some of the early authors, *e.g.* Brettauer and Rubin (1923) suggest, it would clearly be advisable for all patients with a prolapse to be screened by IVU to exclude this complication.

Reported series of cases are not very helpful on this aspect of the problem. Franche *et al.* (1959) reported the presence of dilatation of the upper urinary tract in 11 out of 12 cases (92%) of complete genital prolapse. Racker (1952) had eight cases (33%) out of 24 patients with complete procidentia, while Boveri (1949) reported 17 cases (65%) out of 26 patients with second and third degree prolapse. Everett and Sturgis (1940) found six cases (43%) out of 14 patients with various degrees of prolapse but Guillemin and Cavailher (1948) had only one case (2%) among 60 patients with prolapse of various degrees.

These wide variations in the reported prevalence of the condition must reflect differences in the criteria for selection of cases for investigation but unfortunately these criteria are not usually mentioned.

MATERIAL AND METHODS

In the present trial, cases were selected simply on the basis of being on the waiting list for prolapse repair. Two gynaecologists at the Queen Elizabeth Hospital, Gateshead, and one at the Royal Victoria Infirmary, Newcastle, were asked to submit patients as they arose on their waiting lists for the trial. An IVU was carried out as part of the patient's pre-operative investigation, either as an out-patient or on the day before operation as an in-patient. A specimen of blood was sent for blood urea estimation at the time of the IVU injection. The gynaecologist was asked to complete a *pro forma* for each patient, indicating whether the prolapse was Grade I, II or III. The gynaecologists stressed that prolapse assessed under general anaesthetic in theatre is often more pronounced than in out-patients and provision for re-grading at operation was made on the *pro forma*. The IVU was carried out as follows.

The patient was given a laxative on the day preceding the examination and was starved from midnight. Fifty ml of Urovision (sodium/meglumine diatrizoate—Schering) were injected after a control film had been taken. Five and 15-minute localized and 25-minute full-size films were exposed. No compression was used. Immediately after the 25-minute film the patient was asked to stand or walk for 15 minutes and 40 minutes after injection a full-size erect film was taken. The object of the last film was to see whether descent of the uterus in the erect position resulted in a temporary increase in ureteric compression. The films were assessed for dilatation of the upper urinary tract and for evidence of other urinary tract abnormalities. Any descent of the bladder in the supine or erect position was noted on the report but no attempt at any grading was made as it was felt that this would not contribute anything not detectable on clinical examination.

TABLE I

THE DISTRIBUTION OF THE VARIOUS DEGREES OF PROLAPSE

	No. of patients
Grade I prolapse	11
Grade II prolapse	22
Grade III prolapse	3
Ungraded	1
Total	37

RESULTS

Thirty-seven patients were included in the trial. The average age was 58 years (range 32–76 years). Table I shows the distribution of the three grades of prolapse.

No cases were found to have upper urinary tract dilatation attributable to uterine prolapse.

A surprisingly high prevalence of other urinary tract abnormalities was revealed by the trial. There was one case of mild pelvi-ureteric obstruction, one of previously unsuspected polycystic kidneys in a woman of 35, one duplex right kidney, one case of multiple right renal calculi and two of bilateral chronic pyelonephritis.

Seven patients (19%) had blood urea levels of over 7 mmol/l, including the two chronic pyelonephritics (9 and 14 mmol/l) and the case of multiple right renal calculi (8 mmol/l). No explanation for the raised BU was found in the other four cases, in all of whom the reading was below 10 mmol/l.

CONCLUSIONS

The absence of any cases of upper urinary tract stasis due to prolapse among the 37 patients in the trial establishes that the syndrome is an exceptional occurrence and does not appear in mild form in the lesser degrees of prolapse. Of the 42 patients only three had complete procidentia and even these showed no evidence of ureteric obstruction. However the five cases of the syndrome described at the beginning of this paper all had a complete procidentia and it is clearly advisable for any patient with this degree of prolapse to have full urinary tract investigation. Patients with lesser degrees of prolapse appear not to be at risk and it is unnecessary to submit such patients to routine intravenous urography.

Acknowledgments

I would like to thank my gynaecological colleagues, Mr. D. Tacchi of the Royal Victoria Infirmary, Newcastle upon Tyne, and Mr. D. F. Smith and Mr. W. Y. Sinclair of the Gateshead Hospitals for their invaluable help in sending me cases for the trial and in providing me with the necessary clinical information. I would also like to thank Mrs. K. Murray and Miss S. Stevenson for typing the manuscript.

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Book review

Some Physical, Dosimetry and Biomedical Aspects of Californium-252. Pp. 272, 1976 (Vienna, International Atomic Energy Agency), $18.

This volume gives the Proceedings of an Educational Seminar held at Karlsuke in April 1975, and is made up of a very wide ranging series of papers on the properties and applications of neutron sources made from californium-252. This material is now available in the form of a range of sealed sources which give neutron outputs many orders of magnitude greater than those available from other types of radioactive source. The IAEA is able to lend sources of this type to selected institutions for educational and training purposes.

The proceedings consist of six papers on physics and spectra experiments, two papers on dosimetry, five on radiobiology and medicine, one on radiation protection and three papers on educational aspects. With the exception of the last three, the general form of the papers is to deal rather briefly with experimental techniques, to review the data available in the literature and to give selected bibliographies. The papers on educational aspects give brief outlines of student experiments using californium sources on such subjects as radioactivation, attenuation and shielding measurements and radiation chemistry.

Those sections likely to be of prime interest to readers of this journal are two papers by Piesch on dosimetry, which show a good measure of agreement in the published dosimetry data measured round californium sources in air and in phantom; two papers by Hall which review the data about RBE and OER values, and two papers by Paine, Berry, Wiernik and Stedeford on the use of californium sources for implant therapy. The latter papers give an account of the indications for brachytherapy and the use of γ-ray emitters, particularly iridium wire, for this purpose. Their techniques for using californium sources for this purpose are essentially the same as those used with iridium wire, and details are given of the first 21 patients treated.

While californium-252 sources, which also emit hard γ-rays, have many advantages as neutron sources, they also raise formidable radiation protection problems. This is emphasized in most of the papers and discussed in detail in the paper by Subrahamanian, Venkataraman and Madhvanath.

This volume gives a good introduction to the many fields of application of californium-252. It assumes no special knowledge about this material, but a fairly high level of knowledge about basic neutron physics.

D. Greene.

1977, *British Journal of Radiology*, *50*, 499–503 JULY 1977

Clinical information from medical images. A comparison of two types of ultrasonic image in the detection of focal intrahepatic lesions

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ABSTRACT

If the uncertainty in the diagnosis is measured before and after viewing a diagnostic image, the change in uncertainty is a measure of the information contributed by that image. The formal basis of information theory has been used to calculate the change in uncertainty. These analytical methods have been applied to assess two types of ultrasonic grey-scale image in the demonstration of possible focal intrahepatic lesions.

In times when the capital costs of diagnostic imaging systems are taxing the resources of the health service it is of paramount importance to assess the contribution of each diagnostic test to the management of the patient. Although the experienced diagnostician is able to indicate subjectively the most useful test or the most useful image presentation, objective methods have been formulated not only for indicating the best choice but for measuring the effectiveness of each test (McNeil *et al.*, 1975).

Several methods exist for assessing the quality of diagnostic images. Physical measurements of the optical characteristics (modulation transfer function, quantum mottle and radiographic contrast) may be made but the combination of these factors into a number or function describing the quality of an image is extremely difficult (Rossman, 1974). Rossman (1966) has also demonstrated that the result of a radiographic imaging process is highly dependent on object configuration. Another approach to the problem is to use Receiver Operating Characteristic (ROC) curves (Green and Swets, 1966). An observer is confronted with a randomized series of images, some of which contain a signal and some of which do not. The observer is asked to call each image positive or negative according to whether he sees a signal or not. From these replies, the probabilities of true positive and false positive replies are calculated and may be plotted as a ROC curve. Different imaging systems may be compared by determining, for example, which system has the most true positives for a given false positive rate. This method is particularly suitable for the comparison of imaging systems for which realistic phantoms may be constructed. We believe it has several disadvantages when the images are clinical material. If the observer sees the images in retrospect, however large the total number of images may be, the observer will remember those images he has seen before. This is often a limitation in a radiology department. If the observer decides on the presence or absence of a signal at the time of the examination, the probability of a signal being present depends on the patient and is not the total number of signals divided by the total number of images in the series. Despite these objections, the application of information theory to the ROC curve data by Metz *et al.* (1973) offers a useful approach to the problem of image quality.

Thornbury *et al.* (1975) have recently described the application of Bayes' Theorem to the evaluation of the diagnostic usefulness of excretory urograms. These workers utilized the methods described by Edwards *et al.* (1965) using log likelihood ratios (LLR) to measure changes in subjective estimates of certainty.

The present paper suggests that subjective estimates of probability should be used to describe the uncertainty of a diagnosis at any particular time and that the formal basis of information theory should be used to calculate the change in uncertainty. When comparing two types of image presentation, the quality of an image is judged solely by the information it conveys to the diagnostician. If the uncertainty in the diagnosis is measured before and after viewing the diagnostic image, the change in uncertainty is a measure of the information contributed by the image.

The method is critically dependent on the ability of the clinician to express his clinical judgement in terms of the relative probabilities of the several diagnoses. A number of medical studies have shown that such estimates are valid (Gorry *et al.*, 1973; Gustafson *et al.*, 1971; Ginsberg, 1971).

THEORY

We require an expression for the uncertainty of a diagnosis given estimates of the probabilities of the various alternative diagnoses. Information theory, first described by Shannon and Weaver (1949), provides the basis for quantitating uncertainty in such a case.

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In general, in any system of mutually exclusive situations with probabilities $p_1, p_2, p_3, \dots$ the uncertainty associated with each event or the entropy is defined as

$$H=-p_1\log_2 p_1-p_2\log_2 p_2-p_3\log_2 p_3-\dots$$
$$=-\sum_i p_i\log_2 p_i$$

The general application of this principle is limited by the requirement that the probabilities be mutually exclusive. In the medical field, care must be exercised that the possible diagnoses are in fact mutually exclusive. It is proposed to measure the uncertainty of a system before (H_A) and after (H_B) a diagnostic test. The information contributed by the diagnostic test can then be expressed as $H=H_A-H_B$.

For our immediate purposes, we can simplify the system by considering only two possible diagnoses. In particular, let us consider the case where the diagnostic test determines the presence or absence of a particular lesion. In this case H is a maximum of 1 bit when $p_1=p_2=0{\cdot}5$. These are the probabilities representing the maximum uncertainty of the system. Note that at either $p_1=0$ or $p_2=0$, the uncertainty $H=0$, *i.e.* the diagnosis is certain (Fig. 1). Figure 1 also demonstrates that the value of H is ambiguous; for the two sets of probabilities represented by the points A and B, the uncertainty of the system, H, is the same. Should a diagnostic test have changed the probabilities from point A to point B, information theory states that the uncertainty in the system is the same, but it is obvious that the diagnostic test has contributed information in order to reverse the probabilities. This ambiguity may be overcome by insisting that the change in uncertainty be computed as the point under consideration moves from A to B during the diagnostic test. In this case the information contributed by the test would be

$$H=(H_{\max}-H_A)+(H_{\max}-H_B)$$

Note also that in this particular example the maximum information the diagnostic test can contribute is $H=2$ bits.

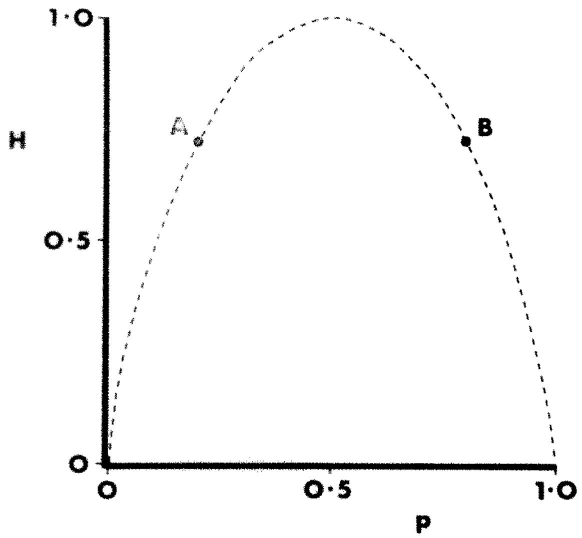

Fig. 1.

The uncertainty H of a system of two possible diagnoses as a function of the probability of one of the diagnoses p.

Clinical Application

These methods of analysis have been applied to the assessment of two types of ultrasonic grey-scale image. The liver was chosen as a suitable organ for study because ultrasonic imaging of liver parenchyma demands grey-scale techniques. The liver scans were carried out for one specific purpose, namely, the delineation of a possible focal intrahepatic lesion. The uncertainty in the diagnosis could therefore be expressed by a probability estimate of the presence of such a lesion.

Clinical material and methods

The 39 patients examined in this trial had suspected liver disease. In addition to those patients with hepatomegaly, jaundice or biochemical evidence of liver disease, patients with proven primary malignancy outside the liver were scanned for the possibility of secondary metastatic liver disease. Prior to this study, no other diagnostic techniques to determine the presence or absence of focal liver disease had been carried out on these patients.

The ultrasonic scanning machine used in this study was a Nuclear Enterprises Diasonograph Model 4102B. The scans were performed using a 2.5 MHz transducer at a pulse repetition rate of 600 pulses per second. Grey scale images were generated by two methods. In the first, images were formed at half-life size from the screen of a Tektronix 611 oscilloscope used in short persistence mode (Fig. 2A). Compound section scanning was carried out by hand and the scans recorded on Polaroid prints. The other type of grey-scale image was produced by connecting the Diasonograph to a Varian 620L computer. The digitized images are produced on a Statos electrostatic plotter; they are life size, contain 16 grey shades and are composed of a matrix of 1 mm by 1 mm cells (Fig. 2B).

Digitized images (Vallance *et al.*, 1976) are acquired simultaneously with the scanning performed for the production of the Polaroid prints, and we therefore have exactly the same input of information from the transducer available for the two types of grey scale imaging.

Before commencing the ultrasonic examination the two radiologists taking part in the trial examined the patient and each then estimated the probability of the patient having a focal intrahepatic lesion. The following question was answered "If you saw 100 patients like this one with exactly the same history and clinical manifestations, how many do you think would eventually turn out to have a focal intrahepatic lesion?"

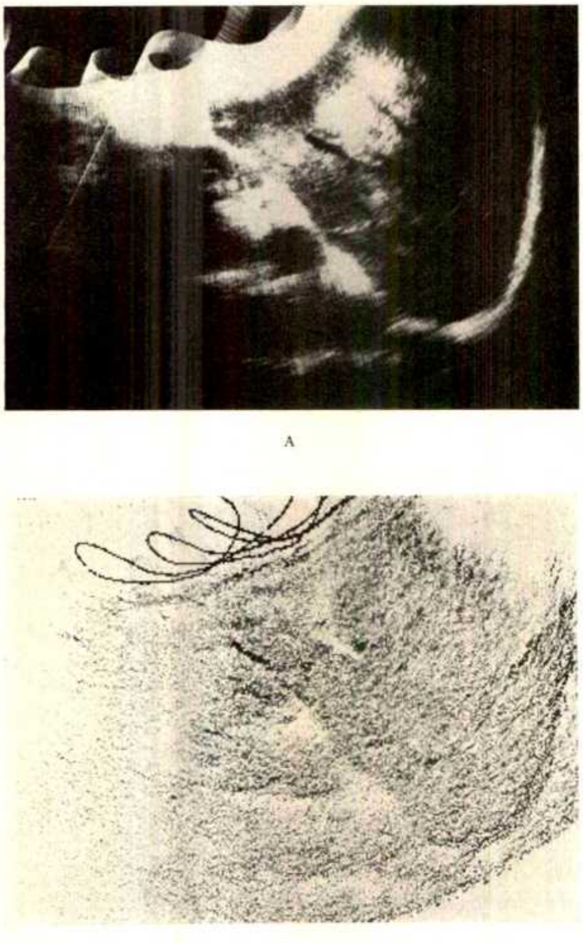

FIG. 2.

A longitudinal section of the right lobe of a liver demonstrating a tumour in the anterior portion (A) Polaroid print; (B) Computer print out.

The patient's liver was then scanned by one radiologist (DAR) who was allowed to use the storage oscilloscope as a guide to the gross anatomy; this permitted only an appreciation of the boundary of the liver. The radiologist was not allowed to view the generation of the grey-scale image or the final Polaroid print. The quality of the Polaroid grey-scale images was monitored by ALE on whose advice unsatisfactory scans were retaken with different ultrasonic or photographic conditions. Grey-scale images and computer images were produced to cover the whole of the liver in longitudinal sections 2 cm apart. Both the computer and Polaroid images derived from each patient were then randomly allocated into one of two groups – group A and group B. In group A, the Polaroid images were examined by DAR who was asked if he wished to revise the initial probability of the presence of a focal intrahepatic lesion. The computer images in group A were examined by GMcC who revised, if necessary, her initial probability. In group B, the order of viewing was reversed. Each reading was done without the observer having seen the other set of images so that finally each radiologist only read one set of images, either Polaroid or computer, per patient. Therefore each radiologist had given two probability estimates per patient, the first (p) before seeing the images, and the second (p^1) revised, if necessary, according to that set of images examined. The information contributed by the test was then calculated to be:

$$H-H^1=-[p\log_2 p+(1-p)\log_2(1-p)]$$
$$+[p^1\log_2 p^1+(1-p^1)\log_2(1-p^1)]$$

Some three months after the completion of the trial, the case records of the 39 patients were reviewed and a decision made as to the "correct" diagnosis. Absolute proof of diagnosis was obtained in three circumstances, namely post mortem, positive biopsy and surgical inspection. In 12/39 patients the "correct" diagnosis was established in these ways. In 21/39 cases the evidence from sources other than those above was strongly in favour of a particular diagnosis. In the remaining six there was insufficient clinical or laboratory evidence to make a diagnosis.

RESULTS

Table I shows the average information contributed by the test calculated for each radiologist and for each image presentation. There is no significant difference between any of the four categories.

TABLE I

Information change (irrespective of final diagnosis)

	Number of patients	Mean information change	±Standard error
DAR Polaroid	15	0.179	0.033
DAR computer	23	0.182	0.022
GMcC Polaroid	22	0.171	0.024
GMcC computer	15	0.130	0.032

TABLE II

Information change referred to final diagnosis

	Number of patients	Mean information change	±Standard error
DAR Polaroid	13	0.187*	0.035
DAR computer	19	0.057	0.043
GMcC Polaroid	18	0.078	0.044
GMcC computer	13	0.110	0.042

*In principle the information change in each row of Table II cannot be greater than that in Table I. In this particular case the mean information change happens to be greater as a result of the exclusion of two patients lacking proof of final diagnosis.

Table II shows the average information change when the changes had been referred to the final diagnosis. For this purpose, the information change was allocated a sign depending on whether the "correct" diagnosis was approached (positive) or whether the test proved to be misleading (negative). The results show that the Polaroid images read by DAR were significantly more useful than any of the other groups.

Discussion

Since there was no significant difference between the groups in Table I, we conclude that each radiologist's opinion was on average altered equally by each mode of presentation. This means that neither radiologist consistently over-read or under-read one image presentation relative to the other. This might have been expected if one observer was deliberately biased against one mode of presentation, that is, he might consistently tend to under-read that mode, and the mean information change would be much smaller.

However, it seems from Table II that DAR derived more correct information from the Polaroid prints than from the computer images. Despite this finding, there was no significant difference between the Polaroid and computer images for the other radiologist GMcC. Although GMcC was relatively inexperienced in the interpretation of both Polaroid and computer ultrasonic images, the mean information derived from both image presentations was significantly greater than zero (about two standard errors). We can therefore infer that GMcC was sufficiently experienced to extract useful information from the ultrasonic scans. We conclude that DAR's accuracy in reading Polaroid prints is probably due to his experience of such presentations. The extent by which this factor has influenced the results was certaintly not appreciated before this trial took place. Ideally a trial of this nature should be conducted using observers equally experienced in both modes of presentation. This state of affairs rarely exists in clinical practice and an observer's performance will always tend to support the technique to which he is most accustomed.

Although this work demonstrates a mechanism by which the value of a diagnostic test to the management of a patient might be assessed, in such a study the personal probabilities of the diagnosis should be assessed preferably by the clinician in charge of the management and not by the radiologist. It is also worth noting that the information content is expressed on an additive scale and is therefore in a suitable form for cost effectiveness studies.

Conclusions

This trial can only be seen as an interim report on the relative assessment of display systems that are under continuous development. The observer experienced in the interpretation of Polaroid ultrasonic images derived more useful information from these images than from the computer images. The less experienced observer performed equally well using either method of presenting the ultrasonic images. In the light of these results it would be unwise to extend the conclusions of this specific trial to other observers without further confirmatory work.

We believe that the method proposed in this paper may be applied generally to select by objective criteria the best imaging system under specified clinical conditions.

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Book review

Abdominal Ultrasound. By Hans Henrik Holm, Jørgen Kvist Kristensen, Sten Nørby Rasmussen, Jan Fog Pedersen and Søren Hancke, pp. 181, 1976 (Copenhagen, Munksgaard: Baltimore, London, Tokyo, University Park Press), £16·00.

This book is based on work performed in the ultrasonic laboratory in the department of surgery of the Gentofte Hospital, University of Copenhagen. The clinical departments and the department of radiology have referred patients to it. Since the establishment of the ultrasonic laboratory in 1965, 15000 abdominal examinations have been carried out. It is stated in the introduction that it is the experience extracted from these examinations that is put forward in the book. This is true in respect to the evolution of the technique of ultrasonic examination of various abdominal organs and of the illustrations of the scans of the normal and abnormal states of these organs. There is, however, little analysis of the clinical value of the information gleaned from all these scans. Those readers who seek statistics on clinical evaluation of diagnostic methods will be disappointed by the scarcity of these in this book. This is indeed a surprising feature, particularly in view of the fact that two of the authors are research fellows in the ultrasonic laboratory. The authors are not radiologists, and this is apparent in that there is little attempt to indicate how radiological and ultrasonic examinations, together with isotope studies, are complementary to each other. For instance, with regard to technique, a complicated method is described on how to determine ultrasonically the angle of inclination of the long axis of the kidneys to the sagittal plane, information which is easily available from scrutiny of the intravenous urography films.

The book suggests the dilemma of authors of ultrasonic texts at the present time of transition from bistable displays (storage technique) to grey-scale displays. The majority of the illustrations are of the former type of display and they are of high quality. The grey-scale illustrations are few in number and they have been produced by a locally-manufactured (and therefore non-standard) mechanical scanner. However, the basic information contained in the two types of display is similar.

The outstanding features of this book undoubtedly are the beautifully reproduced and detailed sectional anatomical drawings of the abdomen and the correlation of the ultrasonic scans with them. They are a real delight to behold and will be of great value to all those who seek to learn and those who seek to improve the interpretation of their scans. Each clinical chapter starts off with an anatomical drawing of the organs to be examined and a verbal description of the anatomy, followed by details of the technique advised for the ultrasonic examination and finally descriptions with illustrations of the normal and of the different abnormalities that can be shown. The liver, biliary system, pancreas, spleen, kidneys, retroperitoneum and adrenals, great vessels, gastrointestinal tract, urinary bladder, female reproductive organs (excluding obstetrics) and extra-organic abscesses and fluid collections are dealt with in separate chapters. A short history of abdominal scanning provides the first chapter and is very fascinating. This is followed by chapters which give simple but adequate descriptions of the basic physics of diagnostic ultrasound and the general principles involved in scanning the abdomen, even including the authors' ideas of the form of the final ultrasonic report. In addition there are useful chapters on ultrasonically guided percutaneous puncture, organ volume determination, errors and pitfalls which may lead to incorrect conclusions and finally indications for ultrasonic scanning of the abdomen.

This is a book, presented in excellent English, which can be highly recommended to all those either in training or of consultant status who have an interest in diagnostic ultrasound.

F. G. M. Ross.

1977, *British Journal of Radiology*, *50*, 504–507

Non-linear bone loss in oophorectomized women

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ABSTRACT

Sequential bone loss in 37 women with bilateral oophorectomy was monitored by radiographic morphometry. The changes in mean width of the cortices of the 2nd, 3rd and 4th metacarpals of both hands were determined using a semi-automated computer-controlled morphometer. It was found that a significantly greater rate of decrease of mean cortical width occurred in those women first observed within three years of the artificial menopause than in the other members of the group.

In a previous publication, we tentatively suggested that in the first few years after the menopause women may undergo a phase of rapid bone loss (Horsman and Simpson, 1975). The suggestion was based on sequential morphometric evidence of a high rate of loss of cortical bone from the metacarpals in women close to the menopause relative to the rate observed in more elderly women. Since the time of that publication, we have continued to monitor bone loss in normal post-menopausal women and in women who have undergone bilateral oophorectomy. Those members of the latter group, who are known not to be suffering from any disorder likely to affect calcium metabolism, form a useful subgroup for study since, in contrast to the natural menopause, the artificial menopause can be dated exactly. In this paper, we present further sequential morphometric data on 37 such women.

METHOD AND INSTRUMENTATION

Cortical bone loss from the metacarpals of 37 women who had previously undergone bilateral oophorectomy (but who were otherwise normal) was measured by the sequential morphometric method of Horsman and Simpson (1975). Duplicate measurements of the total width (TW) and medullary width (MW) of the 2nd, 3rd and 4th metacarpals of both hands were made on two pairs of hand radiographs for each subject. The subjects were studied over time intervals ranging from 1.2 to 9.4 years. In all, the radiographs spanned more than 160 patient–years of observation.

As we have previously emphasized, the observer must measure all the films of each patient at the same sitting because the changes to be detected are small in relation to the possible long-term variation in the observer's judgment of the positions of the cortical boundaries. In order to reduce the labour of the sequential measurements, we recently constructed a semi-automated computer-controlled morphometer and have now abandoned the calipers originally used to make the measurements on the films.

The morphometer, which is run on-line to a PDP-12 computer, is shown in Fig. 1. The film is clamped between a glass plate and an illuminated opaque Perspex screen engraved with a graticule. In the centre of the screen is a rectangular slot within which a slide, engraved with a vertical cursor and two horizontal markers, can be driven from side to side. The position of the vertical cursor is monitored by a precision linear potentiometer which provides a signal to the computer's analogue-to-digital converter. To the right of the film area is a control panel containing a keyboard and display which allows the operator to enter the film dates and to control the general flow of the computer program.

The measurements are made at the midpoints of the diaphyses of the metacarpals. Measurement sites

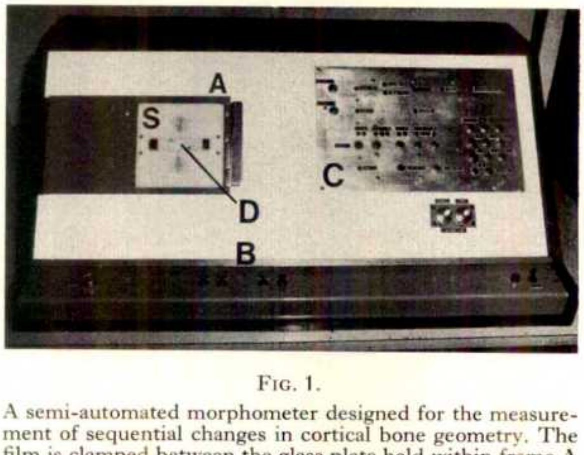

FIG. 1.

A semi-automated morphometer designed for the measurement of sequential changes in cortical bone geometry. The film is clamped between the glass plate held within frame A and the illuminated screen S. The control panel C is on the right and the buttons B controlling the motion of the cursor D are in the foreground.

are lightly marked in pencil on the films as previously described (Horsman and Simpson, 1975). Taking the pairs of films in date order, the following procedure is then carried out:

(1) A number identifying the patient is entered on the keyboard. If the patient already has a magnetic tape file, step (2) is skipped.

(2) A file is created for the data on the specified patient. The patient's sex and date of birth are entered.

(3) The date of the films is entered. (Existing data in the file can be deleted at this stage if necessary.)

(4) The following steps are carried out on the left film then on the right film, taking the 2nd, 3rd and 4th metacarpals in turn:

  (a) The metacarpal is aligned on the graticule with its long axis vertical and with the pencil marks aligned with the horizontal markers on the moving slide.

  (b) The operator positions the vertical cursor on the left periosteal boundary, the left and right endosteal boundaries and right periosteal boundary in turn, stopping at each position to press a button indicating that the computer should sample the position of the cursor.

  (c) The measurements are repeated in the same order without disturbing the film.

(5) The data can be rejected if for any reason the measurements are suspect. Otherwise the data is stored in the magnetic tape file as TW and MW values computed from the cursor positions.

(6) If more films on the current patient are to be measured, steps (3) onwards are repeated. Otherwise the results are evaluated as described below.

Calculations

From the TW and MW values, the mean total width $\overline{TW}$, mean medullary width $\overline{MW}$, and mean cortical width $\overline{CW}$, of the six metacarpals are evaluated for each date. The changes in each variable, $\Delta\overline{TW}$, $\Delta\overline{MW}$ and $\Delta\overline{CW}$ (mm) between the two dates are calculated. $\Delta\overline{CW}$ represents the net change in the amount of bone which occurred during the time interval t (years). The errors of the method have been discussed in full elsewhere for the former technique in which calipers were used (Horsman and Simpson, 1975); the errors of the semi-automated method (< 0.1 mm) are closely comparable to the previously reported values. The errors are absolute; thus the error on the calculated individual rate of change, $\Delta\overline{CW}/t$, varies inversely with t.

RESULTS

The results of the measurements on the oophorectomized women are shown in Fig. 2. This is a cusum plot in which the data for each subject are represented by a short line segment. The projection of the segment on the horizontal axis is the period over which the subject was observed; the projection on the vertical axis is the measured change in the morphometric variable over that period. The segments are joined end to end; thus the final end-point of each line indicates the cumulative change in the morphometric variable for the whole group over the total number of patient-years of observation in the

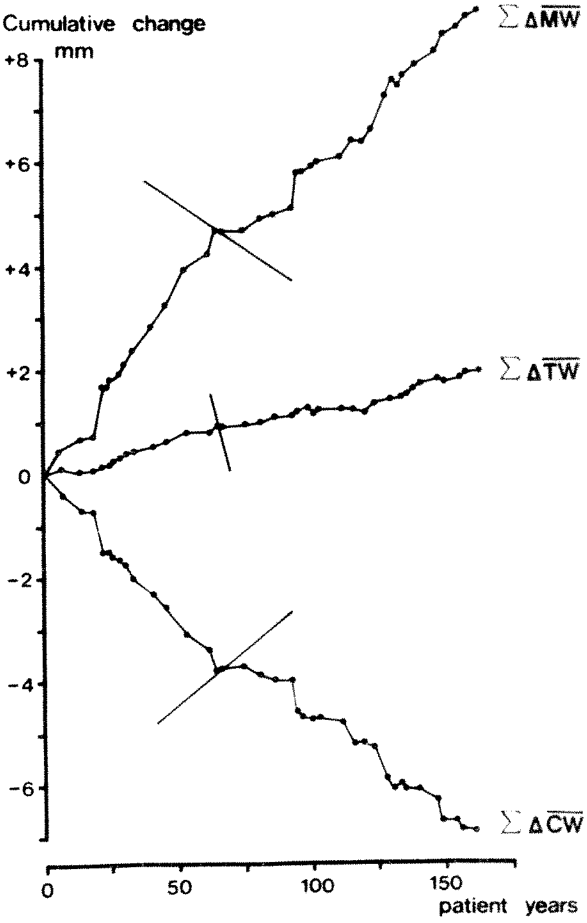

FIG. 2.

Cumulative changes in mean medullary width ($\Sigma\Delta\overline{MW}$), total width ($\Sigma\Delta\overline{TW}$) and cortical width ($\Sigma\Delta\overline{CW}$) of the metacarpals of 37 oophorectomized women. The women have been ranked in order of increasing years since the menopause at the time of the first pair of radiographs. The lines have been arbitrarily divided at three years since the menopause.

study. Although a short observation period carries an inherent risk of large errors in the calculated rate of loss in an individual, on a cusum plot the slope of the line joining the origin and the endpoint is the weighted mean slope of the individual segments where the weighting factor is time. Thus relatively short observation periods in some cases do not necessarily degrade the overall trend of the line.

The women have been ranked in order of increasing years since the menopause in the cusum plot. The first 15 line segments in each cusum line, up to the dividing line, represent the women who were first observed within three years of the menopause. The curvature of the $\Delta\overline{MW}$ cusum line suggests that the rate of increase of $\overline{MW}$ on the whole decreases with increasing years since the menopause, *i.e.* the thickness of the shell of bone resorbed from the endosteal surface each year decreases as the oophorectomized woman ages. Splitting the data at three years since the menopause, the change in slope is highly significant ($P<0.001$); a student's t-test was used with the slopes weighted according to time. The weighted mean rate of change of $\overline{MW}$ in the women < 3 years from the menopause is +0.072 mm/year and in the remaining women is +0.044 mm/year.

It could be argued that if the women had lost a constant volume of bone per unit time from the endosteal surface a curvature with this sign would be expected; as $\overline{MW}$ increased, the shell thickness which would have to be resorbed per unit time would decrease in inverse proportion to $\overline{MW}$. However, it has been shown using the same subjects' data that the cusum of the product $\overline{MW}\,.\,\Delta\overline{MW}$ is itself non-linear ($P<0.001$). Thus we conclude that endosteal bone loss from the metacarpal diaphyses, whether described in terms of shell thickness or cross-sectional area increments per unit time, is a non-linear phenomenon.

The method also reveals the continuing growth at the periosteal surface, demonstrated by the increasing cusum of $\Delta\overline{TW}$. There is no detectable change in the slope of this line with increasing years since the menopause. The rate of increase of $\overline{TW}$ is ~+0.012 mm/year. Although small, the change in $\overline{TW}$ is not negligible; during 162 patient-years of observation $\Sigma\Delta\overline{MW}$ reached +8.93 mm, whereas $\Sigma\Delta\overline{TW}$ reached +1.98 mm. The volume of a thin cylindrical shell of constant thickness and length increases with its diameter. Since $\overline{TW}$ is more than twice $\overline{MW}$ in women close to the menopause, the rate of change of $\overline{TW}$ is a major determinant of the rate of change of cortical bone volume *particularly in the years more than three years from the menopause* when the rate of endosteal bone loss is reduced. It is readily shown that the effect of a constantly increasing $\overline{TW}$ is to accentuate further the decrease in the rate of cortical bone loss (in volume terms) with increasing years since the menopause.

TABLE I

RATES OF CHANGE OF THE DIMENSIONS OF THE METACARPAL DIAPHYSES IN 37 OOPHORECTOMIZED WOMEN

Variable	Rate of change (mm/year) mean ±S.E. (<3y.s.m.: N=15)	Rate of change (mm/year) mean ±S.E. (≥3y.s.m.: N=22)	P
$\overline{TW}$	+0.013±0.0018	+0.011±0.0016	n.s.
$\overline{MW}$	+0.072±0.0062	+0.044±0.0055	<0.001
$\overline{CW}$	−0.058±0.0052	−0.032±0.0050	<0.001

The $\Delta\overline{CW}$ cusum is at all points equal to the difference between the $\Delta\overline{TW}$ and $\Delta\overline{MW}$ cusums. As expected, the slope decreases with advancing years since the menopause ($P<0.001$). The weighted mean rate of change of $\Delta\overline{CW}$ in the women less than three years from the menopause is ~−0.058 mm/year and in the remaining women it is −0.032 mm/year. The mean rates of change of the variables $\overline{TW}$, $\overline{MW}$ and $\overline{CW}$ are contained in Table I.

DISCUSSION

We have recently shown in a controlled trial of oestrogen and calcium therapy in post-menopausal women that a dose of ethinyl oestradiol in the range 25–50 μg is very effective in reducing the rate of cortical bone loss (Horsman *et al.*, 1977). In the untreated controls, the cortical thickness decreased at a rate of ~−0.06 mm/year, a rate much higher than the value we have previously taken as our working normal value for post-menopausal women (−0.04 mm/year) and in fact closely similar to the rate observed in our most recent studies of untreated patients with spinal osteoporosis (Horsman *et al.*, 1976). It was this finding, coupled with the fact that in the trial many of the subjects were oophorectomized women first observed within a few years of the operation, that led us to re-examine the relationship between rate of bone loss and time since the menopause. Our observation of a phase of rapid bone loss after oophorectomy is consistent both with the finding of Garn (1970) that the rate of bone loss in women is maximal at about age 50, and with the observations of Aitken *et al.* (1973). The latter group demonstrated, using direct photon absorptiometry, that mestranol is effective in retarding bone loss in oophorectomized patients when administered up to three years after the operation; that the rate of bone loss was higher in the women observed closest to the operation is apparent in their data although the fact was not highlighted.

It should be noted that the initial rate of loss following oophorectomy must be greater than our data suggest. Due to the smallness of the changes in the cortical width relative to the measurement error, the times of observation are rather long compared with the time over which the rate itself might change. The individual differences which have been measured are chords joining two points on a curve the maximum (negative) slope of which must exceed the slope of the chord.

Bone loss after the menopause, like any other bone loss, is due to an imbalance between bone formation and bone resorption, the latter exceeding the former. We have no evidence that bone formation rate decreases after the menopause, and positive biochemical evidence (hydroxyproline content of fasting urine specimens) that bone resorption is increased (Nordin *et al.*, 1975). However, our morphometric data indicate that there is an adaptive mechanism which resists the sacrifice of the skeleton. Hypertrophy of regions subject to increased stress is well known, *e.g.* vertical trabeculae in the vertebral bodies hypertrophy as the horizontal struts are resorbed (Atkinson, 1967). Hypertrophy implies increased bone formation; yet the morphometric data indicate that periosteal bone formation is not stimulated in the metacarpal. Thus the diminishing rate of bone loss with the time must be due to a fall in the rate of bone resorption. This might occur as a consequence of a partial restoration of the plasma oestrogen levels through increased secretion or conversion of androstenedione from the adrenals.

Whatever the mechanism, that there is a phase of rapid bone loss following the artificial menopause is now clear. Although it is the rapid loss which excites attention, it is perhaps the subsequent decrease in the rate of loss which is the more interesting. It might be an inability to reduce the rate of bone resorption in some individuals which eventually leads to crush fractures of the spine.

ACKNOWLEDGMENTS

We would like to thank Professor M. S. F. McLachlan, Head of the University Department of Radiodiagnosis, Leeds, and H. B. Bentley, Principal of the School of Radiography, Leeds General Infirmary, for their assistance in the radiographic aspects of this work.

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NORDIN, B. E. C., GALLAGHER, J. C., AARON, J. E. and HORSMAN, A., 1975. Post-menopausal osteopenia and osteoporosis. *Frontiers in Hormone Research, 3*, 131–149.

Book review

Diagnosis and staging of cancer. A radiologic approach. By R. J. Steckel, and A. R. Kagan, pp. xx + 376, 1976 (Sussex, W. B. Saunders & Co.), £16·50.

In their preface the authors state that this book is intended as a guide to clinicians who treat cancer patients and is not a radiological text. In some ways they are being too modest because, on the whole, it covers the subject fully and those of us who work in the cancer field know that radiologists are very grateful for guidance about what information is really needed for the clear demonstration of tumours, their extent and spread in order to allow informed decisions to be made about treatment.

One may not always agree with what is said as for instance: "All patients suspected of having gastric malignancy should have a barium enema in order to detect tumour extension" and "a skeletal survey is essential for complete examination of the patient". Again this is referring to carcinoma of the stomach where bony metastases are very rare and one suspects that such advice is a little over-enthusiastic as a routine. Also it is a pity that tumours of the testicle are dismissed in one paragraph when radiology plays such a prominent part in the successful management of these tumours in many centres.

However, this is an excellent book and will be of value to all those interested in oncology.

J. S. MACDONALD.

1977, *British Journal of Radiology*, 50, 508–512

Static and dynamic imaging with indium-III labelled Bleomycin in the localization of squamous cell neoplasia

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ABSTRACT

Fifty two cases of squamous cell carcinoma were studied using indium-111 labelled Bleomycin. Theoverall accuracy of localization by static imaging alone was 80%. Detection of lung and gynaecological tumours was most consistent, while oesophageal tumours were the most commonly missed. Imaging within a few hours of administration of the radiopharmaceutical was found to be as effective as imaging at the recommended time of at least 24 hours. Inflammatory lesions giving false positive scans could be differentiated from tumour tissue by the technique of dynamic imaging. Maximum activity occurred in tumour tissue on average ten minutes after the peak for normal tissue. This difference was used to improve the detection of known tumours to 90%.

The use of Bleomycin, an antineoplastic antibiotic, chelated to indium-111 for the localization of tumours was first described by Merrick *et al.* (1973). Indium-111 emits γ rays of energies 179 and 247 keV which are suitable for imaging with rectilinear scanners or gamma cameras, and has a convenient half-life of 2.8 days. Other short lived radioisotopes have been investigated but the highest tumour-to-blood ratio was obtained with the indium label (Thakur *et al.*, 1974). Cobalt-57 has also been used (Suzuki *et al.*, 1974; Rasker *et al.*, 1975) but the long half-life of 270 days requires collection of urine and faeces to minimize environmental radiation hazards.

There have been many studies reported of the use of labelled Bleomycin for tumour localization (Merrick *et al.*, 1973; Grove *et al.*, 1974; Suzuki *et al.*, 1974; Rasker *et al.*, 1975; Merrick *et al.*, 1975). However, Bleomycin has a particular affinity for squamous cell tissue. Labelled Bleomycin should therefore form a particularly good radiopharmaceutical for the localization of squamous cell carcinomata.

Experimental evidence shows that maximum concentration of Bleomycin in squamous cell tissue occurs about 15 minutes after intravenous injection (Thakur *et al.*, 1972), after which it is rapidly deaminated. Thakur *et al.* (1972) postulated that indium, though released from Bleomycin, is deposited in the tumour. The best compromise between high tumour-to-blood ratio with minimum physical decay of the radioisotope is 72 hours and it is generally recommended that imaging be started at least 48 hours after intravenous injection.

However, indium-Bleomycin scans have certain disadvantages. By 24 hours post injection there are high concentrations of indium in the liver, bone marrow and kidneys. Activity in the kidneys accumulates rapidly and appears to remain fixed (Thakur *et al.*, 1972) but there is a slower accumulation in the liver and bone marrow. This activity can mask uptake in tumours adjacent to these organs. A further disadvantage is the accumulation of activity due to non-malignant causes such as pneumonia (Merrick *et al.*, 1975), which can lead to a false positive interpretation of the scan.

In this paper the technique of dynamic imaging was used to study the early uptake of ^{111}In Bleomycin in normal, inflammatory and malignant tissue in an attempt to improve tumour detection and differentiate causes of increased uptake.

MATERIALS AND METHODS

Patients with histologically proven primary and secondary squamous cell carcinomata under treatment in the Department of Chemotherapy, Bradford Royal Infirmary, were investigated in the Department of Medical Physics.

A total of 52 patients (32 M: 20 F), mean age 60 years (range 34–82 years), were investigated during 1974–75. *Bleomycin, 1.5 mg labelled with 2 mCi ^{111}In, was given intravenously. The radiation dose to liver, spleen, kidneys and bone marrow has been estimated by Williams *et al.* (1975) to be about 1 rad/mCi to each organ.

All patients had whole body scans using a J and P Multipoise scanner with 3: 1 minification, at 24 hours and some also at three hours and 48 hours. When appropriate 1:1 scans or gamma camera scintiphotos from the Nuclear Data Radicamera were also obtained. Dynamic studies of the uptake of ^{111}In Bleomycin were performed using the gamma camera and its associated Nuclear Data Med II computer. By careful use of anatomical landmarks (Mason, 1975), sequential data were obtained up to 48 hours post injection. Patients were injected while positioned in front of the gamma camera and frames of data were acquired at one minute intervals for 45 minutes, then at 60 and 120 minutes. In six cases further frames of data were taken at intervals up to 48 hours post injection. Where possible, regions of interest were selected over the primary site, secondary site(s), heart, liver and an area designated "normal". The normal region was chosen to correspond anatomically to the tumour site, *e.g.* if the tumour was on the right lung then the normal region was selected over the equivalent zone of the left lung. Venous blood samples were taken for simultaneous blood clearance measurements.

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*Bleomycin Lundbeck

By use of the computer's region of interest facility, the changes of activity in specified areas were measured, *e.g.* tumour, heart, liver and a comparable normal area. All data were corrected for decay of the radioisotope. Uptake of activity was calculated by the "excess counts" method (Najean *et al.*, 1975). The total activity detected over a tumour is the summation of activity in the vascular phase and uptake of ^{111}In Bleomycin in malignant tissue. If it is assumed that the initial count rate measured at one minute post injection is due only to activity in the blood then the count rate due to vascular activity at later times may be calculated by reference to the blood clearance curve. Counts in excess of the predicted vascular activity represent accumulation of the radiopharmaceutical by the tumour. The excess counts are usually expressed as a percentage of the total counts obtained over the tumour. By the same method the excess counts can be calculated for non-tumour tissue. This is a convenient method for demonstrating the dynamic uptake of activity in a particular organ when activity from surrounding organs or vascularity contribute to the detected count rate.

RESULTS

The 52 patients investigated had a total of 73 known separate squamous tumours, either primary or metastatic lesions. Table I is a summary of the accuracy of squamous cell tumour detection by static imaging. In our experience tumours in the chest and the pelvic region were accurately localized. The single false negative scan repeatedly failed to demonstrate ^{111}In Bleomycin concentrating in the tumour of the right main bronchus. Only one instance of a previously unknown metastasis was found in this series. The presence of this tumour was confirmed at post mortem. Ten head and neck deposits were probably missed due to their small size. Tumours of the oesophagus are very difficult to detect because of the high concentrations of indium in the liver, spleen and bone marrow at the time of imaging. The overall accuracy of squamous cell tumour localization was 80%. It should be noted that about one in five patients had areas of false positive uptake on their scans. The most common cause was pneumonia.

TABLE I

ACCURACY OF DETECTION OF SQUAMOUS CELL CARCINOMATA BY STATIC IMAGING

Site	True+VE	False−VE	Total	False+VE
Head/Neck	26	10	36	
Bronchus	12	1	13	9
Lung	12	0	12	
Oesophagus	1	4	5	
Pelvis	7	0	7	1
	58	15	73	10

Number of patients = 52. Overall accuracy = 80%.

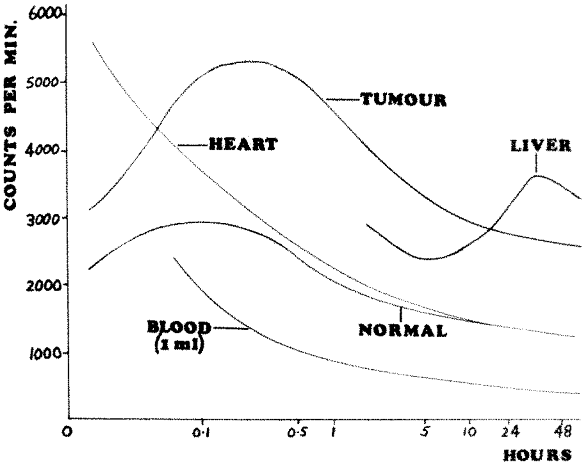

FIG. 1.

Uptake of ^{111}In-Bleomycin with time. The tumour was in the right bronchus and the normal region was selected over the left chest. The liver curve follows the heart curve until about four hours.

Figure 1 is an example of the results obtained during dynamic imaging from the six patients who were studied from the time of injection up to 48 hours later using the gamma camera and computer. It was found that activity in normal squamous tissue always peaked earlier than that in the tumour region. Activity in primary and secondary tumours in the same patient always peaked at the same time. The liver and bone marrow showed accumulation after about four hours.

Figure 2 is an example of the accumulation of ^{111}In Bleomycin in malignant and normal squamous tissue after subtraction of vascular activity from the total activity detected. Table II shows a significant improvement in the detection of head and neck tumours by dynamic imaging. The tumour of the bronchus that was not detected by dynamic imaging is the same case that is listed as a false negative scan in Table I.

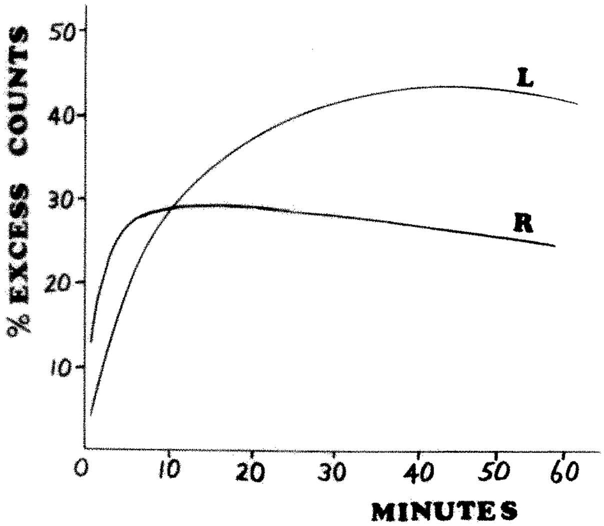

FIG. 2.

Accumulation of ^{111}In-Bleomycin in a tumour of the left lung and in the normal right lung after subtraction of vascular activity.

TABLE II

COMPARISON OF DYNAMIC AND STATIC IMAGING

	True +VE		
Site	Dynamic	Static	No. of Tumours
Head/Neck	11	6	11
Bronchus	3	3	4
Lung	2	2	2
Oesophagus	1	0	2
	17	11	19

No. of patients = 17.

The average time for normal squamous tissue to reach peak concentration for the 17 patients studied by dynamic imaging was nine minutes (standard deviation 3.5 minutes) and for malignant tissue 18.5 minutes (standard deviation 7.5 minutes). The mean time difference between normal and tumour peaks was 10.5 minutes (standard deviation 7.5 minutes).

The time of imaging is usually based on the tumour-to-blood ratio of concentration of activity. However, tumour detectability on a scan is determined by the ratio of count rate over the tumour to the count rate over the area adjacent to the tumour. Figure 3 shows both the tumour-to-blood ratio and the tumour-to-normal tissue ratio for the data in Fig. 1. It can be seen that the tumour-to-normal ratio remains almost constant after one hour. This would suggest that tumours should be equally well visualized on an early scan, *i.e.* one to three hours after injection, as on the conventional late scan 24 hours or longer after injection. Thirteen patients had both early and late scans, and 16 out of a total of 19 tumours were detected. In no case was a tumour detected on an early scan that was not detected equally well on a late scan and vice versa. Early scans have the advantage of no liver and bone

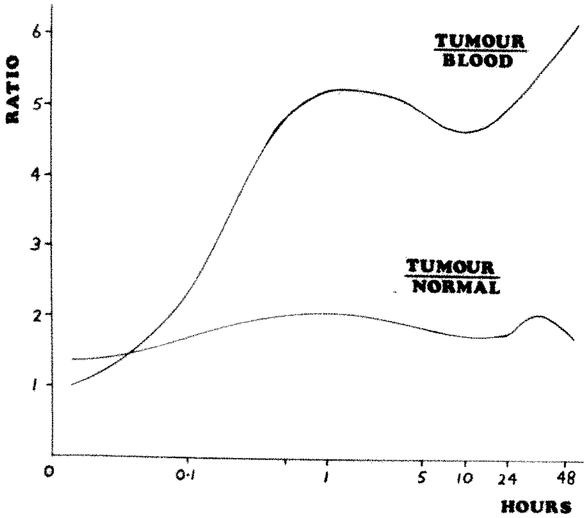

FIG. 3.

Ratios of activity in tumour: blood and tumour: adjacent normal tissue.

marrow activity, but the disadvantage of higher heart, kidney and bladder activities than the late scans.

The dynamic uptake of ^{111}In Bleomycin was also studied in five patients with pneumonia. It was found that the count rate from the region of interest selected over the pneumonic area decreased at the same rate as the count rate over the heart after about one minute. Figure 4 shows the results obtained from a patient with a tumour of the right bronchus and pneumonia of the right lower zone. The left lung was normal. This pattern was found in the five patients studied who had pneumonia.

DISCUSSION

Static imaging using labelled Bleomycin will detect about 65% of malignant tumours (Suzuki *et al.*, 1974; Merrick *et al.*, 1975). The detection rate for squamous cell carcinomas reported in this paper was 80%. A disadvantage of ^{111}In Bleomycin is the high incidence of false negative and false positive static scans. False negative scans were defined as those scans which failed to demonstrate concentration of the radiopharmaceutical at the site of a known squamous cell tumour and false positive scans as those scans which showed increased concentration at a site subsequently proven not to be an area of malignancy.

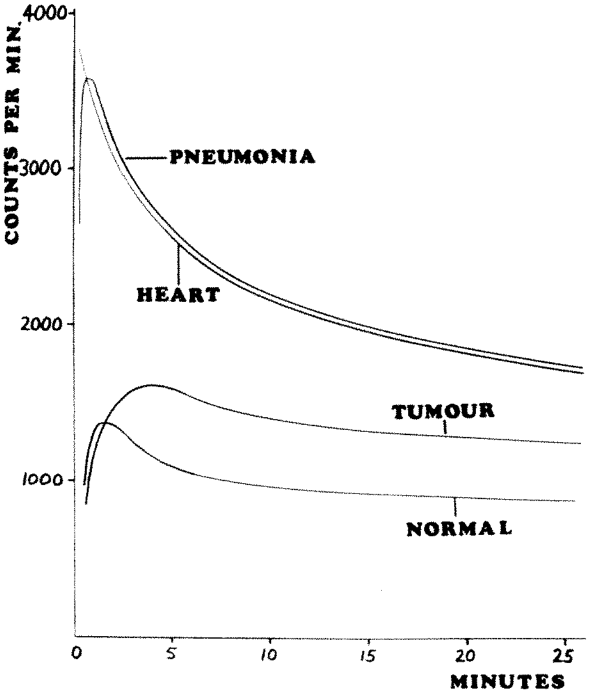

FIG. 4.

Dynamic curves obtained in a case of pneumonia in the right lower zone.

False negative scans can be due to several factors, *e.g.* the tumour may be smaller than the resolution of the detector or it may not accumulate activity to a detectably higher concentration compared to adjacent tissue. Using ^{111}In Bleomycin false negative scans occur most frequently when the tumour is sited in the larynx, mediastinum or oesophagus. It is probable that uptake in these tumours is masked by the high activities of ^{111}In in bone marrow and liver.

Dynamic imaging from the time of injection has demonstrated the rapid accumulation of ^{111}In Bleomycin in normal and malignant squamous tissue before significant detachment of the indium label from Bleomycin had occurred. It was also found that malignant squamous tissue accumulated Bleomycin over a longer period than normal tissue and to a higher concentration. This was a consistent pattern noted in all patients having dynamic studies. The investigation of patients with pneumonia has indicated that the higher concentrations seen on static scans are due to increased vascularity of the pneumonia area and not simply an increased concentration of Bleomycin in the lung. Dynamic imaging may therefore be used to differentiate causes of increased uptake.

Monitoring the concentrations of activity in malignant and normal squamous tissue and in the blood has shown that it is not essential to wait 24 hours or more before imaging. Early scans show high vascular concentration but no liver and bone marrow activity, whereas late scans show the opposite features of low vascular background but high concentrations in the liver and bone marrow. Although in this series early scans did not improve tumour detection, theoretically it would appear that the detection of oesophageal tumours could most likely be obtained by a combination of dynamic imaging and a static scan at about six hours when the combined blood, liver and bone marrow activities are at a minimum.

Dynamic imaging during the first hour following injection utilizes information on the comparative rate of accumulation of the radiopharmaceutical in specific areas which is not available by conventional static imaging alone. It is a more sensitive method of detecting small tumours, particularly of the head and neck, than static imaging and offers the possibility of assessing pathology and so reducing the high incidence of false positive scans found with ^{111}In Bleomycin.

Acknowledgments

We wish to thank Messrs. Lundbeck Ltd., and the M.R.C. Cyclotron Unit, Hammersmith Hospital for supplies of ^{111}In Bleomycin. We also wish to thank the staff of the Medical Physics Department for their assistance in this study and Miss Robinson for preparation of the manuscript.

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Book review

Radiation Protection for Medical and Allied Health Personnel, N.C.R.P. Report No. 48, pp. v+72, 1976 (Washingt on D. C., National Council on Radiation Protection and Measurements), $4.50.

This report, as the title suggests, is intended for those personnel who have not received any formal training in radiological protection but who, nevertheless, find themselves working permanently or temporarily in regions of the hospital where ionizing radiations are employed. It is intended for laboratory technicians, nurses, aides, orderlies, messengers, secretaries and porters, to mention but a few of the hospital personnel who might be concerned to the point of "almost pathological fear" whether their working environment "will decrease libido or even produce sterility".

The report goes to great lengths to make the subject palatable to those who have little or no knowledge of ionizing radiation or to those who have not had the benefit of a scientific training. It gives, for instance, a brief but lucid description of radioactive disintegration and avoids mathematical terminology to the extent that the Curie is defined as 37 billion disintegration per second (an American – English dictionary should be available). Likewise, it deals with the usual misconceptions that, for instance, a personnel monitor does not protect you and that exposure to X or γ rays does not make you radioactive.

The report covers all the major aspects of radiological protection, dividing the text into "X-ray Departments", "radioactive nuclides" and "laboratories" instead of the more familiar separation of diagnostic radiology, radiotherapy and nuclear medicine. It also gives in brief the biological effects of ionizing radiation and includes sections on "the morgue" and disposal of radioactive waste. Some of the terminology used and data given are different from those to be found in the D.H.S.S. *Code of Practice* and there is a mixture of SI and imperial units.

Before purchasing this report or, as we are urged to do, "placing copies in such locations as to be readily available to anyone desiring the information it contains", there are certain questions to be answered. First, will it educate and so allay the fears of the intended reader? The answer is simply that, in some cases, it may do so but the majority for whom it is intended will find the scientific content more than they can cope with. The report does suggest, however, that it may encourage the reader to seek out his "radiation protection supervisor" when he has a problem. If it does this, then it will have succeeded although one would not like to be the supervisor who is asked by the ward orderly to explain to her the meaning of isomeric transition. The second question is, will this American publication be of value in the UK? As has been said, some of the terminology is different from that to be found in the UK *Code of Practice* and so, since it is intended to make all clear to the non-radiation worker, this could present some confusion.

It is doubtful whether ward orderlies, messengers, guards, porters, janitors and maintenance men will ever read such a publication no matter how many copies are on display.

T. H. E. Bryant.

1977, *British Journal of Radiology*, 50, 513–517

Sublethal damage in cells of the mouse gut after mixed treatment with X rays and fast neutrons

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ABSTRACT

The effect of combining X ray and neutron irradiations on cell survival in the mouse intestine has been investigated. The irradiations from the two beams were given within minutes or at most a few hours of each other when recovery from sublethal damage was not always complete. The results show that cells surviving the first dose of radiation have accumulated the same amount of recoverable sublethal damage regardless of whether that first dose was with X rays or neutrons. The rate at which the sublethal damage is shed is the same after X rays or neutrons. It is reasoned that there is less sparing of damage by fractionation of neutron dose compared with fractionation of X ray dose not because there is less recovery from sublethal damage after neutrons but because there is relatively more lethal damage; the recovery from any sublethal damage is the same as if it were from X rays. If X rays and neutron doses are separated by times long anough to allow the full repair of sublethal injury then the combined effect is simply additive.

There is evidence that benefits may be obtained in the treatment of some tumours by neutron therapy (Catterall *et al.*, 1975). Should these benefits be clearly established for the treatment of some of the most commonly occurring primary tumours, the pressures on suitable neutron sources for these patients would be considerable. This pressure might be alleviated by using neutrons for part of the treatment and combining this with photons. This practice is already used in Houston and in East Germany. The results from these centres are, as yet, insufficient to make any assessment of the practice. In designing mixed treatment schedules it would be useful to have scientific information on the effects of combining X or γ rays with neutrons, on whether the effects are simply additive or whether there is interaction.

Early work of Barendsen (1961) suggested that the combined effects of X-rays and α particles on cell survival of human cells *in vitro* were simply additive. Recent work of Railton *et al.* (1975) and Durand and Olive (1976), both using Chinese hamster cells, has suggested there was some interaction when neutrons and X- or γ-irradiations are combined and that damage was not simply additive. In these studies irradiations with the different beams were given within minutes or at most a few hours of each other when recovery from any sublethal damage was not always complete. In a study of the effects of a mixed schedule of daily fractions of X rays or 14 MeV neutrons on the small intestine of mice, Hendry *et al.* (1976a) found the effects of the two radiations were simply additive. In this latter case, with an interval of one day between fractions, recovery from any sublethal damage was probably complete before the subsequent irradiation.

The stem cells of the small intestine show a considerable ability to accumulate and repair sublethal damage after X irradiation and a smaller accumulation and repair of sublethal damage after neutron irradiation. Cell survival can easily be assessed in the small intestine using the crypt count technique (Withers and Elkind, 1970). In this paper we describe the effects of combining X rays and neutrons on crypt survival in the mouse jejunum, with doses separated by a few minutes to a few hours so that the effect of recovery from sublethal damage in mixed irradiation schedules over this period can be evaluated.

METHODS AND RESULTS

CFLP female mice weighing 25–30 g were given whole body irradiation while breathing oxygen. The animals were killed four days later and parts of the small intestine were fixed in Bouin's fixative. Sections of the jejunum 5 μm thick were cut and stained with haematoxylin. The number of crypts per circumference in transverse section was counted in four sections taken at 0.5 cm intervals. Three to six mice were used at each dose level. The X-irradiations were given with 250 kV X rays filtered through 0.5 mm Cu and 1 mm Al, which gave a HVL of 1.3 mm Cu. The fast neutrons were produced by bombarding a beryllium target with 16 MeV deuterons from the Hammersmith cyclotron. The neutron dosimetry has been described previously (Bewley and Parnell, 1969).

The number of crypts per circumference in unirradiated mice was 110 ± 1.8 (S.E.). Animals were given a first dose of 540 rad of neutrons or 1250 rad of X rays. These doses reduced the number of crypts

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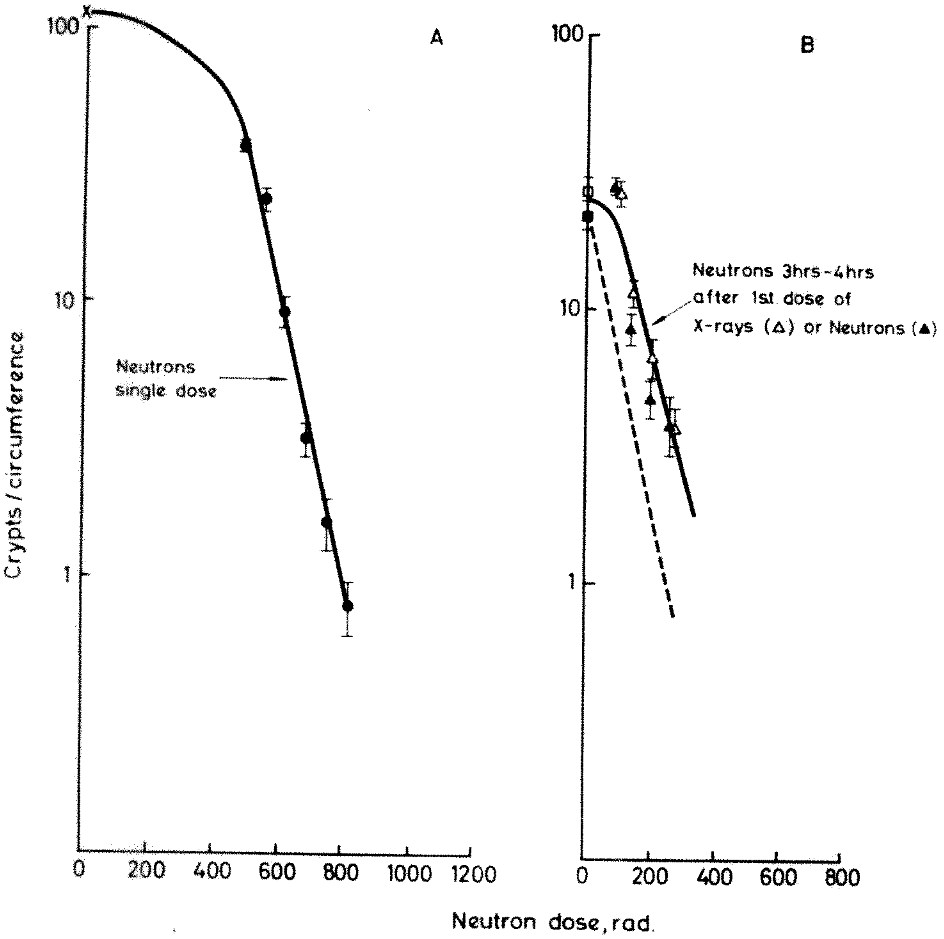

Fig. 1.

(A) shows the number of crypts per circumference in the mouse jejunum after single doses of neutrons, and (B) shows the number of crypts after a second dose of neutrons given three to four hours after a first dose of 540 rad of neutrons (▲) or 1250 rad of X rays (△). (×) crypts in unirradiated jejenum, (■) crypts after 540 rad neutrons, (☐) crypts after 1250 rad X rays. All points shown with standard errors.

to about 20 to 25 crypts per circumference in each case.

The effect of giving a second dose of neutrons three to four hours after the first dose of X rays or neutrons is shown in Fig. 1B. It can be seen from Fig 1B that the crypt survival level produced after this second dose of neutrons is not different regardless of whether the first dose was given with X rays or neutrons. The dotted line in Fig. 1B is the survival curve to second neutron doses given immediately following the first neutron dose of 540 rad, *i.e.* it is the single dose neutron survival curve (Fig. 1A) from 540 rad to higher doses. It can be seen that the slope of this single dose neutron survival curve and the final slope of the second neutron survival curve are not different.

In Figs. 2B, C and D are shown the survival curves to a second dose of X rays given 15 minutes, two hours and three to four hours respectively after a first dose of either X rays or neutrons. It can be seen that the response to the second dose of X rays is similar regardless of whether the first dose was given with X rays or neutrons (Figs. 2C and D). The survival curve to single doses of X rays is also shown (Fig. 2A). The dotted lines in Figs. 2B, C and D are the survival curves to a second dose of X rays given immediately after the first dose of 1250 rad, *i.e.* they are the single dose X ray survival curves from 1250 rad to higher doses of X rays. There is clearly an increasing separation of the second dose X ray curve from the single dose (dotted) curve as the time between fractions is increased and this separation is the

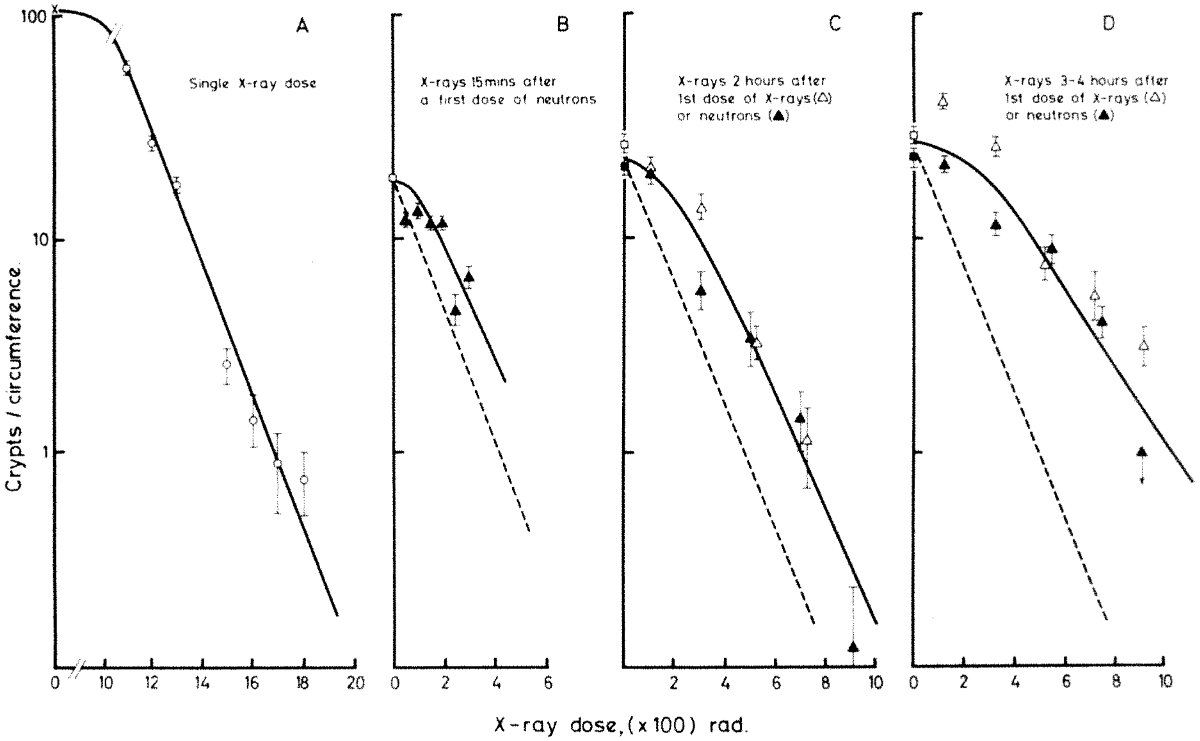

FIG. 2.

(A) shows the number of crypts per circumference in the mouse jejunum after single doses of 250 kV X rays. (B) shows the number of crypts after a second dose of X rays given 15 minutes after 540 rad of neutrons (▲). (C) shows the number of crypts after a second dose of X rays given two hours following a first dose of 540 rad of neutrons (▲) or 1250 rad of X rays(△). (D) shows the number of crypts after a second dose of X rays given three to four hours following a first dose of 540 rad of neutrons (▲) or 1250 rad of X rays (△). (×) crypts in unirradiated jejunum, (■) crypts after 540 rad of neutrons, (□) crypts after 1250 rad X rays. All points shown with standard errors.

same regardless of whether the first dose was given with X rays or neutrons.

DISCUSSION

Radiation damage in cells can be divided into lethal damage and sublethal damage. Operationally, lethal damage results in an exponential relationship between cell survival and dose while sublethal damage implies an accumulation of damage before the final energy deposition event is able to kill the cell, so that a shouldered cell survival curve is obtained. Elkind and Sutton (1959) demonstrated that if the dose was divided into fractions, recovery from sublethal damage could take place between the fractions. However a shouldered cell survival curve does not necessarily indicate that there will be recovery from accumulated sublethal damage. The shoulder could represent a multiplicity either of targets or hits, from which there is no recovery. The effect of fractionation on survival from these three different types of damage is illustrated in Fig. 3.

The proportion of lethal and sublethal injury, which is LET dependent, varies with cell type and with the condition of the cell. The observations reported in this paper are concerned with the accumulation and recovery from sublethal damage in the cells of the small intestine after X rays and neutrons. At the dose levels used for the first dose with both X rays and neutrons all the surviving cells have probably accumulated a maximum amount of sublethal damage. The results suggest that the surviving cells have accumulated the same amount of recoverable sublethal injury regardless of whether the first dose was given with X rays or neutrons, and also that the rate at which this sublethal injury is shed is the same regardless of the initial radiation. This is shown by the fact that the additional dose of X rays required to overcome the recovered sublethal injury inflicted by a first dose of X rays or neutrons is the same.

It has previously been shown that recovery from irradiation injury in the gut after low LET radiation

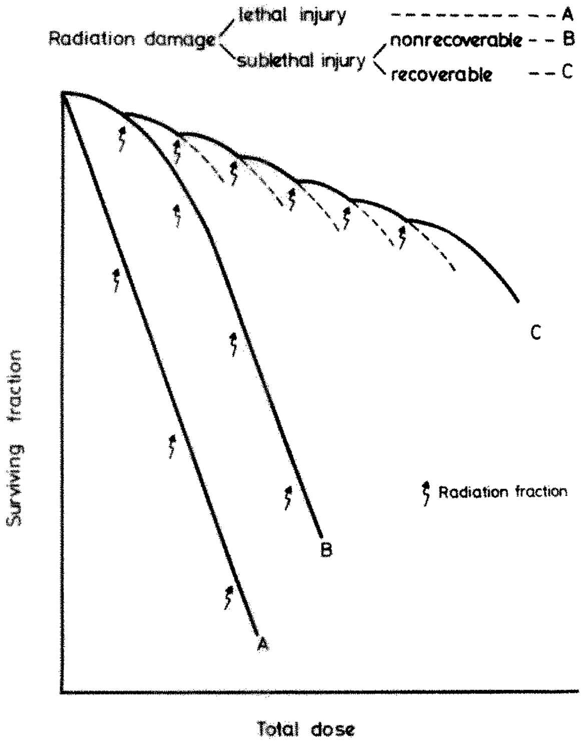

Fig. 3.

The effect of fractionation of dose on cell survival from the three types of radiation injury—lethal injury, non-recoverable sublethal injury and recoverable sublethal injury.

has a very rapid component so that measurable recovery can be observed within 10–14 minutes (Hornsey and Alper, 1966). The present observations show that an equally rapid component occurs in the recovery after neutron irradiation. The time course of recovery in terms of the additional X ray dose required to give a standard level of damage is compared in Table I with previous values for low LET radiation. The increase in this additional X ray dose with time is similar regardless of whether the first dose was given at high or low LET. Clearly, if sufficient time elapses between irradiations for full repair of sublethal injury to take place, the effects of the radiation (in terms of lethal injury) are additive regardless of whether the radiations were X rays plus X rays or neutrons plus neutrons, or X rays plus neutrons, as was shown by Hendry *et al.* (1976b). If insufficient time elapses between irradiations for full repair of sublethal injury, there will be some interaction. The degree of interaction will depend on the relative amounts of lethal and sublethal injury for the different combinations of radiations.

It has been shown that fractionation of neutron dose gives less sparing of damage in tissues than

TABLE I

Additional photon dose required to overcome recovered damage ($D_2 - D_1$)

Test	Radiation		Time between doses				Source
	1st dose	2nd dose	10–15 min.	2 h	3–4 h.	12–24 h.	
3 crypt survival level, jejunum	250 kV X rays Neutrons	250 kV X rays 250 kV X rays	120 rad 120 rad	270 rad	520 rad		This paper
LD$_{50}$/4–5 days (30 crypts per circumference)	6 MeV electrons	6 MeV electrons	100 rad		400 rad	400 rad	Hornsey and Alper, 1966 Hornsey, 1970
	250 kV X rays	250 kV X rays			400 rad		Hornsey and Vatistas, 1963
10^{-2}–10^{-3} surviving fraction of jejunum	8 MV X rays			300 rad		300 rad	Hornsey, 1973
LD$_{50}$/5 days				250 rad		450 rad	

fractionation of X ray dose (Hornsey *et al.*, 1975; Hendry *et al.*, 1976b) and this has sometimes been explained as being due to less recovery from sublethal damage after neutrons compared with X rays. The results reported here suggest that this explanation is incorrect and that the lack of sparing observed is due primarily to the fact that a large part of the initial injury in neutron irradiation is lethal injury or non-recoverable sublethal injury. The recovery from any recoverable sublethal injury deposited by neutrons is the same as if it had been deposited by low LET radiation. The relationship between the logarithm of cell survival and dose can usually be described by a linear component αD and a squared component βD^2. Rossi (1976) has pointed out that when the effects of γ rays and fast neutrons are compared α is found to differ considerably but β is fairly constant. The results reported here support this observation.

In the tissues the amount of recoverable sublethal injury relative to lethal injury after neutron irradiation varies considerably, as is demonstrated by the different values for (D_2-D_1) for the Hammersmith neutrons. (D_2-D_1) for damage to the jejunum is 30–100 rad (Hornsey, 1973), for radiation induced pneumonitis 100–200 rad (Field and Hornsey, 1974), and for necrosis in mouse tails about 350 rad (Hornsey *et al.*, 1977). Even in the latter case, where the highest value for (D_2-D_1) has been obtained, there is little further sparing of damage if the neutron dose is divided into more than two fractions. This seems to be due to the fact that at low doses or low doses per fraction the contribution to biological damage from the high LET components of dose is relatively greater (Hornsey *et al.*, 1977). The lethal damage produced by these high LET components will be cumulative while there will be some shedding of the recoverable sublethal damage produced by the lower LET components of dose. For equal levels of tissue damage therefore the greater the fractionation of neutron dose the greater the contribution of lethal injury relative to recoverable sublethal injury. At the doses per fraction used in therapy much of the tissue damage will be due to single event killing even in those tissues where considerable recovery from sublethal injury can be demonstrated in split dose experiments with neutrons. In these cases the effect of combining X rays and neutrons will be additive with little sparing of damage by fractionation of the neutron dose and the normally expected sparing by fractionation of X ray dose.

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Technical note

A rapid method for the preparation of stable $^{99}Tc^{m}$–urokinase

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(*Received October, 1976 and in revised form March, 1977*)

The importance of detecting deep vein thrombosis in post-operative patients and others at risk is well established. The most reliable routine techniques are labelled fibrinogen tracer and contrast venography, but both have important disadvantages. Fibrinogen is taken up by forming thrombus and therefore it has to be injected before the patient is at risk and may not give a positive result for two to three days after thrombus formation. It is not valuable above the upper thigh and results in unnecessary radiation to patients who do not develop thrombi. Ascending contrast venography is highly accurate in the veins that are filled but does not show the soleus plexus or the deep pelvic veins. A small but definite hazard is involved as with all contrast injections. Intraosseous venography to show the deep pelvic veins is generally unacceptable as a standard investigation.

Urokinase, which is a fibrinolytic enzyme extracted from the urine, has the attraction of being non-antigenic, being incorporated into formed and forming thrombus and not carrying the risk of hepatitis virus (Rhodes *et al.*, 1972). The methods of labelling urokinase with $^{99}Tc^{m}$ tried so far have been chemical, *e.g.* using stannous chloride (Lin *et al.*, 1971; Millar and Smith, 1974); all give a relatively low yield of labelled enzyme. An electrolytic method is described which is both simple and reliable, and gives a high yield of stable, labelled enzyme.

METHOD OF PREPARATION

Each electrolytic cell is prepared as follows. Two lengths of zirconium wire (99.87% pure; Goodfellows Metals, Cambridge) about 7 cm long—enough to reach the bottom of a 10 ml capped injection vial with an excess of about 2 cm above the cap—are cleaned by dipping in hydrofluoric acid until obviously clean. Then, after thorough rinsing in tap and distilled water, they are pushed through the cap of the injection vial using a "T018" transistor pad above the cap to support the electrodes and increase the insulation provided by the cap. The unit is then autoclaved (115°C for 30 min) in a double wrapping of polythene and can be stored for at least a month before use (the effect of longer storage has not been investigated). The electrodes can be re-used until they become too small, despite the 2 cm excess, to complete the circuit with the fluid contents of the prepared cell. They must be cleaned and prepared as described above each time they are used.

For labelling urokinase, 1.0 ml of 0.2 normal hydrochloric acid (B.P. injection standard), 1.5–2.5 ml of $^{99}Tc^{m}O_4^-$ in saline (3–5 mCi) and 5000 Ploug units (Ploug and Kjildgaard 1957) of urokinase injection (Leo Laboratories, Middlesex), dissolved in a convenient volume of 0.55 ml "water for injection", are mixed in the cell vial. A direct current of 40 mA is passed for 2 min through the cell which must be thoroughly shaken throughout electrolysis either in an ultrasonic bath, in which it is easier to maintain a constant current, or a shaker, After electrolysis, the solution should be shaken for at least a further 5 min and then filtered into a sterile 10 ml capped injection vial through a 0.22 μm membrane and the latter washed with about 2 ml of 0.9% sodium chloride solution for injection. This filtered solution (plus washings) is ready for injection.

QUALITY ASSAYS

The labelled enzyme preparation was subjected to several chromatographic analysis procedures, *in vitro* tests and animal studies to assess:

(a) its radiochemical purity and stability,
(b) *in vitro* uptake and
(c) acute toxicity, blood clearance and organ distribution.

(a) A sample from each preparation was rapidly developed on 5×1 cm strips of Whatman No. 1 paper in 85% methanol solvent. Free pertechnetate was found to be only 15% or less of the total activity of the sample and the preparation appeared to have a wide margin of stability, up to 24h.

A second chromatographic system used was saline elution down 21×0.6 cm columns of medium "Sephadex G25" gel. The eluate, 17–20 ml, was

TABLE I

G25 SEPHADEX GEL/SALINE CHROMATOGRAPHY OF $^{99}Tc^m$-UROKINASE PREPARATION USING:

% total sample activity in:	Zr electrodes	Sn electrodes
gel column fractions	89.9	83.4
(column top fraction)	(77.7)	(51.8)
eluate TcO_4^-	6.3	3.9
eluate peaks other than TcO_4^-	none	11.7 (2 peaks)

collected in 1 ml fractions, the gel divided into approximately 1 ml samples at the end of elution and counted at the same time as the eluate fractions to give total sample activity. Table 1 shows the profile of the product compared to that produced using tin electrodes (see discussion).

(b) Early in the development of the preparation technique the uptake of activity into thrombi was tested. Aliquots suitable for injection were incubated at 37–39°C with approximately 2 ml samples of coagulated human blood, three samples per time period of 15, 30, 45, 60, 90 and 120 min. Uptake into the saline-washed clots, relative to the total radioactivity added, was measured. In three experiments, uptake, which did not change after the first observation period of 15 min, was 66%, 63.3% and 61.8%.

(c) No signs of acute toxicity were evident when 0.5–1.0 ml of the preparation was slowly injected intravenously into the tail or jugular vein of 30 rats—the human dose is normally about 4 ml. The organ distribution of the labelled enzyme was also studied in rats. At various times after injection, the animals were killed with an overdose of anaesthetic (25% urethane), a blood sample taken immediately from the heart, and then all the individual organs taken including stomach, gut, urine and bladder.

By means of gamma camera scintigraphy it was found that the pH of the preparation greatly influenced the distribution. When the electrolysed solution (which has a pH of 1.0) was treated with phosphate buffer, immediate precipitation of a white flocculent material was seen and, as expected, the buffered preparation showed significant accumulation of radioactivity in the rat lungs. When left unbuffered and slowly injected intravenously at the low pH maintained during electrolysis, only the rat liver showed concentration of radioactivity – *e.g.* with one preparation 63.8% and 64.2% of total dose in the liver of two rats at 5 h. The kidneys were the only other organs showing concentration of activity, at 4.6% and 7.5% respectively in these same two animals, with respective total blood activities of 4.1% and 8.5%.

To study the blood clearance of the preparation in rats, the jugular vein and carotid artery of each rat was cannulated and, at time 0, a weighed amount of preparation injected through the jugular cannula. 0.1 ml samples of blood were taken via the carotid cannula at 15, 30, 45, 60 and 90 min, 2, 3, 4 and 5 h after injection. After each sample 0.1 ml saline was used to clear the cannula.

The blood clearance was found to be multi-exponential. Stripping the curves obtained from five animals using a double exponential programme appeared to give adequate definition of the replotted curves. An initial fast clearance with a half period of 15.2±3.7 min (s.d.) and slow component of 347± 110min were obtained. The blood background was reduced to 22.1% (±3.2%) of the original activity within the hour. In humans therefore, imaging can be started 40–60 min after injection.

DISCUSSION

The method of labelling the urokinase was modified from that devised by Benjamin *et al.* (1969) for labelling albumin. This method included the use of a platinum electrode in a zirconium crucible; the chemistry is discussed by Steigman *et al.* (1974). An electrolytic method using zirconium was chosen for several reasons, particularly the radiochemical purity and stability of the product and its ease of preparation. The use of stannous chloride to reduce Tc (VII) in pertechnetate to Tc (IV) (which is believed to be the oxidation state of technetium during most of its labelling reactions (Hambright *et al.*, 1975)) is the most common method of preparation of the majority of $^{99}Tc^m$– labelled radiopharmaceuticals. However, for labelling urokinase and albumin the yield is low because of the sensitivity of stannous chloride to oxidation by atmospheric oxygen and oxidants in the generator eluate. Elution down an ion-exchange column is necessary during preparation when stannous chloride is used; even then the labelled enzyme is stable for only 30 min (W. T. Millar, 1976, personal communication). Therefore, because of the common use of tin in radiopharmaceuticals and the resulting wide experience in its toxicity etc., tin electrodes were tried (Gil *et al.*, 1976) as an alternative to zirconium at one stage in the development of the technique. It was hoped that the electrolytic production of Sn(II) ions in the presence of the enzyme might solve the problem of radio-chemical impurities. However, as mentioned earlier, this was not seen to be the case since the enzyme showed a more fragmented profile when Sn electrodes were used including impurity peaks in the eluate fractions. The radiochemical impurity was also reflected in the distribution of the tin-catalysed preparation in rats. Increased bladder activity was invariably seen with the tin preparation. This would be expected if the impurities were partially reduced TcSn complexes since these tend to be rapidly excreted by the kidneys (Cox, 1976). However, rapid excretion of the radiopharmaceutical via the kidneys is not peculiar to this method of preparation in either rats or humans. Similar results, including high liver uptake of radioactivity, have also been obtained in mice and dogs by Rhodes *et al.* (1972) who labelled the enzyme using an iron-ascorbate method.

With the zirconium electrolytic method, all the constituents of the labelling "kit" can be readily prepared in stable, sterile form for storage until use and can be combined and electrolysed easily under aseptic conditions to give a stable product of useful radiochemical purity.

It was calculated by Benjamin *et al.* (1969) that 0.242 mg of zirconium was released during electrolysis for each coulomb of current passed. Therefore 40 mA for 2 min releases 1.16 mg of zirconium most of which would be injected into the patient. However, the toxicity of zirconium has been shown to be low (Chapman *et al.*, 1970).

In a limited clinical application, urokinase venography has been found to correlate extremely well with contrast venography and clinical assessment. The results of this study will be reported elsewhere (E. R. Davies, 1977, personal communication).

Conclusion

A simple and reliable electrolytic method of labelling urokinase with ^{99}Tc^{m} is described. This compound has important applications in rapid detection of formed or forming deep vein thrombi, and may also be useful in detecting pulmonary emboli.

Acknowledgments

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JULY 1977

Case reports

Ultrasound and Hodgkins disease of the spleen

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(*Received December, 1976 and revised form March, 1977*)

CASE HISTORY

A housewife, aged 65, was admitted for investigation of fever and left upper abdominal pain. She had been well until four months previously when she developed a sore throat followed by persistent fever which occurred each day, especially in the evening. The symptoms became worse and she then developed aching in the shoulders and wrists without swelling, and pain in the left upper quadrant of the abdomen, worse on deep inspiration radiating to the left shoulder. She felt ill and had lost 10 kg in weight.

EXAMINATION

Temperature 38°C. The spleen was palpable and tender 4 cm below the costal margin. There was no significant lymph node enlargement and the liver was not palpable. The rest of the examination was normal.

INVESTIGATIONS

Hb. 11.6 gm/dl., WBC 16×10^9/L—neutrophils 75%, lymphocytes 19%, ESR 21 mm/hour. Chest X-ray at first showed a raised left diaphragm, later with linear shadowing above it. A radioisotope liver scan showed a normal hepatic uptake, but the spleen was enlarged with a large central filling defect.

Ultrasound examination (Fig. 1) was performed using a Diasonograph 4102 series machine with grey-scale attachment. Scanning of the spleen revealed a large relatively transonic area in the upper pole of the spleen 4 cm in diameter, and smaller transonic areas at the lower pole and in the mid zone suggestive of tumour infiltration.

PROGRESS

The fever and splenomegaly were thought to be due to splenic abscesses or to tumour in the spleen. At laparotomy the spleen was enlarged and was found to be largely replaced by tumour with the major tumour masses in the areas defined by the ultrasound examination. Histology revealed Hodgkin's disease of mixed cellularity type.

Post-operatively a bone marrow biopsy was normal but lymphography showed para-aortic nodes which were enlarged and contained filling defects. Chemotherapy with mustine, vincristine, procarbazine and prednisone was begun with some improvement.

DISCUSSION

The investigation of the spleen and its pathology has always presented a problem to the clinician. Radioisotope scanning ^{99}Tc^{m}, while giving an overall impression of splenic tissue, is often incapable of showing detail and cannot differentiate between solid and cystic lesions.

The normal spleen is visualized ultrasonically as a highly transonic structure and at low sensitivities only its outline and a few echoes from the hilar region are registered (Holm, 1975). At high sensitivity the splenic tissue fills in with uniform echo dots. Taylor and Milan (1976) correctly diagnosed 15 out of 20 patients with Hodgkin's disease and other lymphomas pre-operatively by their increased size

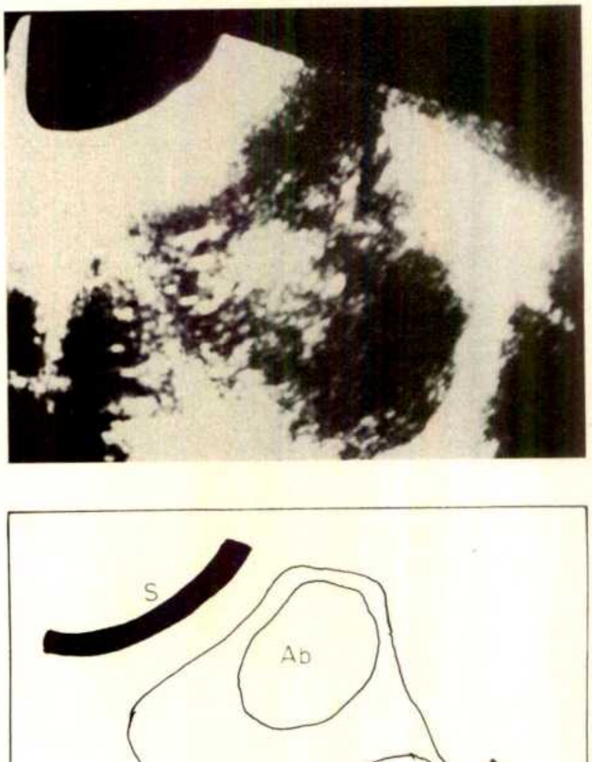

FIG. 1

Parasagittal ultrasound scan showing spleen (Sl) containing abnormal areas (Ab). The skin (S) is also shown.

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1977, *British Journal of Radiology*, 50, 522–523

and decreased echo amplitude. Investigative staging procedures are important in the management of Hodgkin's disease (Glatstein *et al.*, 1969).

In the patient described here, the site and size of splenic tumour deposits was accurately located preoperatively. Ultrasound can be a useful non-invasive technique for the diagnosis of Hodgkin's disease of the spleen.

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A foreign body granuloma simulating a pericardial cyst: an unusual case report

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(*Received October, 1976*)

This report presents an unusual case of paracardiac mass which was revealed ten years after heart surgery. The mass could not be distinguished radiologically from a pericardial cyst. At surgery it was found to be a foreign body granuloma containing a piece of surgical sponge.

CASE REPORT

A 31-year-old white man was admitted to this centre on September 19, 1974, complaining of palpitations and dull precordial pain.

Ten years previously the patient had had a Starr-Edwards aortic prosthesis and mitral commissurotomy for aortic and mitral rheumatic valve disease.

On admission, his temperature was 36°C, pulse 88 per minute, sinus rhythm and the blood pressure was 120/80 mm Hg. He was a well nourished white male. Systemic review was unremarkable.

ECG showed S-T and T waves alterations consistent with left ventricular hypertrophy.

Laboratory examination showed anaemia with a haemoglobin of 10.7 g but was otherwise normal.

Chest X ray revealed a large mass in the right cardiophrenic angle apparently fused with the cardiac border, measuring about 10 cm in diameter. This was interpreted as probably a pericardial cyst, secondary to the cardiac surgery.

Surgery, through a sternotomy, disclosed a rounded mass attached to the right side of the heart. It measured about 10 cm in diameter.

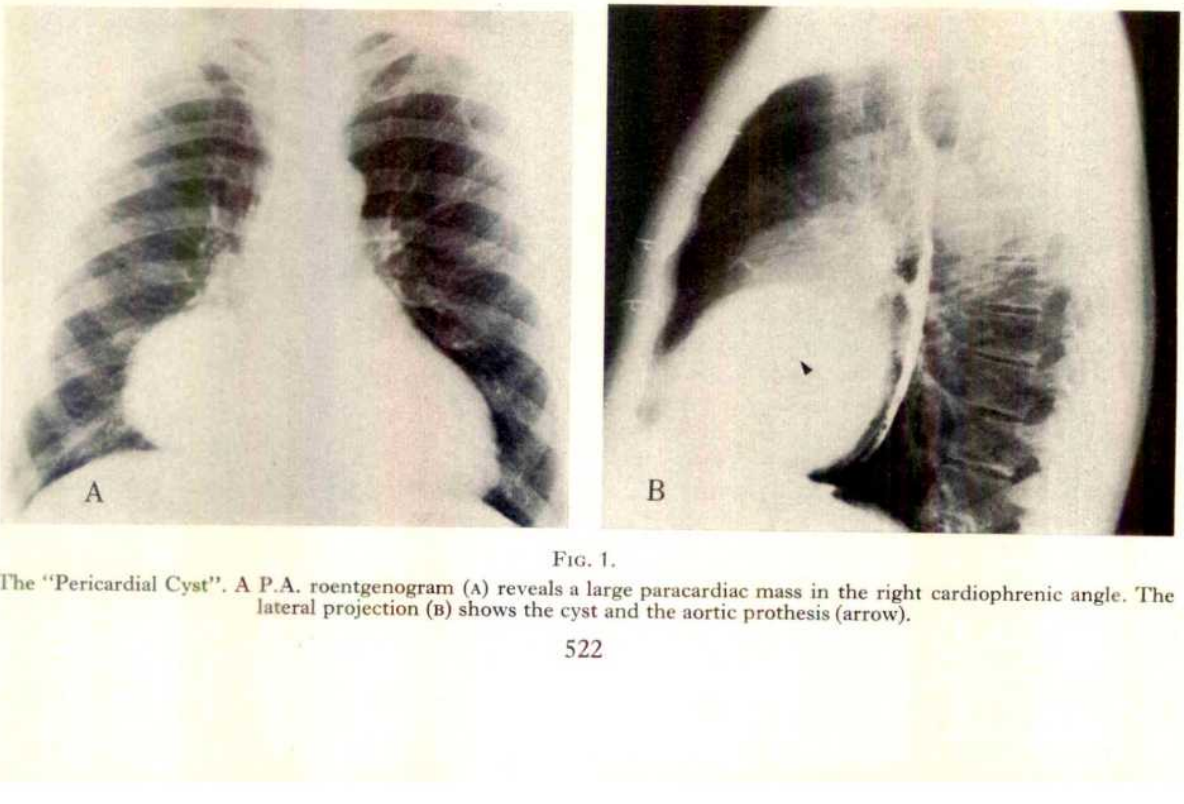

FIG. 1.

The "Pericardial Cyst". A P.A. roentgenogram (A) reveals a large paracardiac mass in the right cardiophrenic angle. The lateral projection (B) shows the cyst and the aortic prothesis (arrow).

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The mass was incised and found to be a cyst containing a surgical sponge. The cyst was removed and dissected out from the auricular border with the local pericardium, preserving the phrenic nerve.

Following surgery his symptoms disappeared completely and he has been free of symptoms for the last year.

Pathology examination showed a piece of surgical sponge about 5 × 5 cm surrounded by greyish caseous material.

Microscopic examination revealed a typical foreign body granuloma with giant cells, lymphocytes and monocytes surrounding homogeneous acellular material.

DISCUSSION

We did not find any similar case described in the literature. It is difficult to make a radiologic differentiation between this kind of cyst and congenital or post-surgical cysts (Deenadayalu and Tuuri, 1974; Pokorny and Idriss, 1974). However, a percutaneous transthoracic needle biopsy might have given the correct diagnosis (Klatte and Yune, 1972).

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Unusual, isolated seminoma metastases to the lung

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Metastases following adequate treatment of stage I seminoma of the testicle are rare, and they usually appear within the first 24–30 months following diagnosis. The lung is the commonest site, frequently bilateral, rounded, well defined opacities growing rapidly if untreated.

We report a case of solitary lung metastasis with unusual appearance and behaviour. No similar case has been traced in the literature.

CASE HISTORY

A 41-year-old male presented with a three month history of painless right scrotal heaviness and swelling. On examination he was found to have a painless irregular swollen right testicle 10 cm in diameter. Exploration of the right scrotal contents was carried out through a right inguinal incision, and orchidectomy was performed.

Histology revealed seminoma of the classical type with invasion of the tunica vaginalis, rete testis, epididymis as well as vascular invasion.

Chest X-ray, bipedal lymphography and IVP were all within normal limits. Accordingly he was staged as stage I seminoma of the testicle, and a post-operative radiotherapy course to the para-aortic and right pelvic nodes was given using a 6 MeV linear accelerator and 3484 rad midplane dose in 22 fractions over four-and-a-half weeks, which was well tolerated.

He was well for the following 40 months, and on a routine check-up a small confluent left upper zone lung shadow was found. This suggested an inflammatory rather than metastatic lesion, possibly tuberculosis or aspergillosis. At this time the patient was in excellent health with no evidence of recurrence, and it was decided to watch this carefully.

In the following 14 months this shadow increased only very slightly in size, and radiologically still appeared very unlike metastasis (Fig. 1). It was decided to investigate this further. Total body ^{67}Gallium scan showed no evidence of metastasis. Whole lung tomography (Fig. 2) showed an irregular opacity with multiple areas of translucency within it and a central more solid lesion, with the remainder of both lung fields clear.

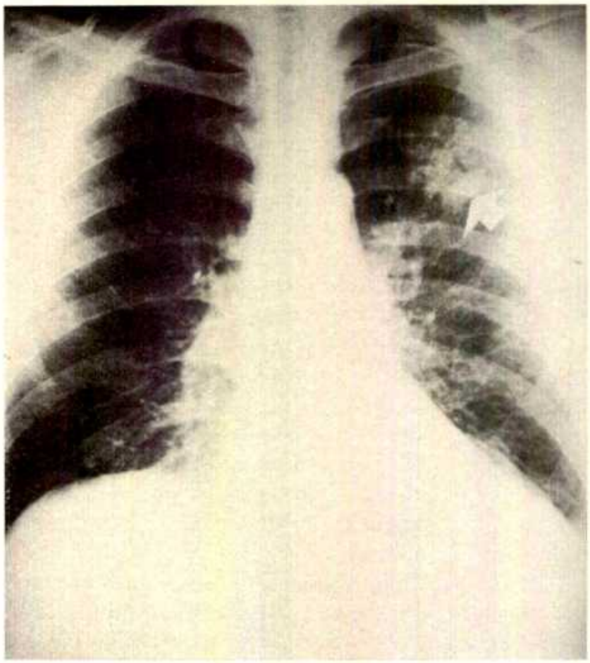

FIG. 1.

Chest X-ray showing left upper zone irregular lung lesion suggesting inflammatory rather than metastasis from seminoma of the testicle.

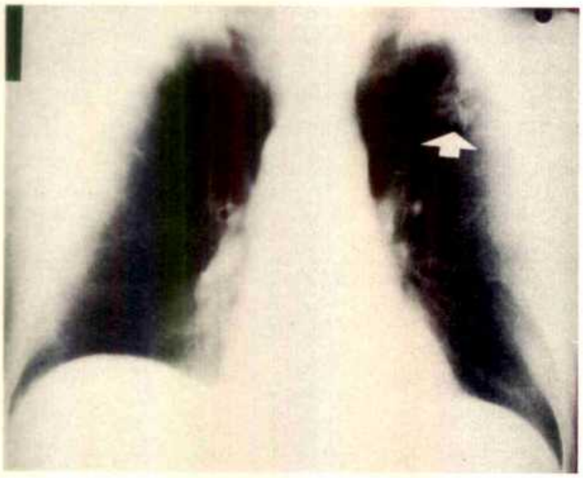

FIG. 2.

Lung tomography showing left upper zone irregular opacity with multiple areas of translucency and a solid centre.

Tuberculin testing was positive (1 = 10000), and sputum examination failed to demonstrate AFB, or M. Tuberculosis on culture.

Bronchoscopy, bronchial washing, and brush smears were negative for endobronchial lesions, neoplastic cells or AFB, and four cultures were negative for M. Tuberculosis.

Percutaneous lung needle biopsy was carried out, and the material obtained was compatible with metastasis from seminoma of the testicle. Left upper lobectomy was performed and the histology of the resected lobe showed classical seminoma with fibrous septa containing numerous inflammatory cells, consistent with origin from testicular seminoma (Dr. K. M. Grigor and Dr. A. M. Mackay).

DISCUSSION

Recurrences or late metastasis from stage I seminoma of the testicle, adequately treated by inguinal orchidectomy and post-operative irradiation to the para-aortic and homolateral pelvic nodes, are very rare. The cure rate for such lesions approaches 100% (Peckham and McElwain, 1974; Van Der Werf-Messing, 1976).

Smithers *et al.* (1971), reporting on the radiotherapy treatment of tumours of the testicle, found that metastases or recurrences usually take place in the first two years following the initial diagnosis. In a large series of stage I seminoma treated in this hospital there were no metastases or recurrences, while in this patient metastases appeared 40 months following diagnosis.

The classical appearance of seminoma metastasis to the lung are usually multiple, rounded, well defined, frequently bilateral lesions, growing rapidly if not treated (Macdonald, 1976). By contrast our patient had a solitary diffuse lesion, growing very slowly. The radioisotope ^{67}Gallium localizes extremely well in seminoma deposits (Paterson *et al.*, 1976), but in this case the lung deposit failed to show up on scanning.

Surgical excision of isolated lung metastasis from testicular tumours is known to produce long-term remissions. To our knowledge, almost all the reported series so far have dealt with isolated secondaries from tumours other than seminoma of the testicle (Asvall *et al.*, 1957; Effler, and Blades, 1948; Ehrenhaft *et al.*, 1958; Hood *et al.*, 1955; Parker, 1958; Patton and Mallis, 1959; Rees and Cleland, 1971; Rowlandson, 1958; Schell, 1961).

Seminoma is an extremely radio-sensitive tumour and the use of irradiation to treat visceral metastasis is recommended by some authors (Patton and Mallis, 1959; Peckham and McElwain, 1975). Such metastases are also cured by alkylating agents (Mackenzie, 1966).

Because of the localized nature of this metastasis, the absence of any evidence of other spread, and the very slow growth rate it was felt that left upper lobectomy was the best treatment for this patient. Fourteen months following this operation the patient now remains in excellent health, with no evidence of recurrent or metastatic disease.

ACKNOWLEDGMENTS

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Book reviews

Matériel et techniques en Radiologie Pédiatrique. Eds. P. Jouve and J.-F. Huguet, pp. 314, illus., 2nd edn, 1976 (Paris, L'expansion Scientifique), F.160.

This book is based upon a series of papers given by a large number of French paediatric radiologists at a symposium organized by Professor Jouve in Marseilles in May 1972. In the second edition, published in 1976, the material has been revised and further sections added in the light of the further advances. It is aimed at the general radiologist who, in the course of his work, has to examine children. The late Professor Lefebvre states in his foreword that in France in 1973 general radiologists were responsible for between 50 and 75% of all paediatric work, a figure which is probably valid for Great Britain also.

The result is a useful compendium of "special procedures" as they may be applied to children, with some discussion of the ways in which apparatus may be designed or adapted to paediatric requirements. Of particular interest are the sections on the value of 70 or 100 mm camera techniques, on the use of thoracic impedance in chest radiography for triggering exposures at peak inspiration and on the investigation of urinary infections. The papers on various aspects of cardiological investigation and on the estimation of skeletal maturation are also valuable.

For English-speaking radiologists, the language problem and the different nomenclature and dose measurement as applied to contrast media and anaesthetic agents is a considerable disadvantage. Other defects are the lack of a proper index and the almost universal use of positive prints for the illustrations. There is no reference to methods of arthrography, nor to pneumoperitoneum in the otherwise useful section on the investigation of intersex.

Some of the statements made in the book will strike British readers as slightly odd. It would be of interest to know if the reactions of French neonatal paediatricians or orthopaedic surgeons to the statement that radiology is the only method of confirming or disproving the presence of congenital dislocation of the hip is likely to be as picturesque as that of their Anglo-Saxon colleagues undoubtedly would be.

It is considered by those of us who have the good fortune to visit radiological centres abroad, that one of the chief advantages of this lies in the chance to observe unfamiliar techniques and to compare them with our own practice; a process which tends to stimulate stagnant thought processes.

Those whose knowledge of French is sufficient to the task will similarly find not a little of interest and benefit from reading this book, but it must be admitted that it is likely to appeal to only a very limited readership in this country. However, for any radiologist who is contemplating taking advantage of our membership of the E.E.C., to practise paediatric radiology in France, this would be an essential guide to the methods employed and to the expressions and idioms they may expect to meet with on the other side of the Channel.

I. R. S. GORDON.

Cancer in Children, Clinical Management. Edited by H J. G. Bloom, J. Lemerle, M. K. Neidhardt, and P. A. Voûte, pp. xiv+317, 121 figs., 1975 (Berlin, Heidelberg, New York, Springer-Verlag), DM 34·50.

This well-produced book is admirably light and easily handled. In fact, if it were not for the difficulty of concealing its uncompromising title, it would make good reading for train journeys.

It is aimed at doctors working in the general cancer field and for paediatricians who wish to become more familiar with recent approaches to the special problems of paediatric oncology. Postgraduates studying for higher examinations will also find this a useful guide.

The four editors are members of the International Society of Paediatric Oncology (SIOP) and were set the task of producing this book by the Patient Care Committee of the International Union Against Cancer (UICC).

The book is divided into two main parts, general chapters and special chapters. The general chapters are perhaps the more valuable part, as they deal with principles of management which are unlikely to alter greatly over the next few years. The special chapters, dealing with different types of tumours or tumours of particular sites, suffer from the fact that modern therapy is advancing too quickly for the information with regard to chemotherapy to be really up to date.

The first two chapters are uninspiring and that on pathology tends to degenerate into lists of tumour types with insufficient information to be of real interest. The chapters on surgery and radiation therapy are particularly well done with sufficient detail to be of some practical use. A simple account of tumour kinetics and the pharmacology of cytotoxic drugs, is given in the section on chemotherapy, but this chapter would have been improved by expansion.

The editors have not imposed a uniform pattern of presentation on the authors of the special chapters, and with such a large number of contributors this has led to a confusing and irritating inconsistency of chapter sub-headings.

This book is recommended for its many good chapters. It is hoped that it will make its readers more aware of the improved outlook for children with cancer which is resulting from the teamwork of doctors working in the various disciplines involved in the management of paediatric oncology.

JILL A. BULLIMORE.

1977, *British Journal of Radiology*, 50, 526–527

Short communication

A non-invasive technique for gastric motility measurement

By D. N. Bateman, B.Sc., M.B., M.R.C.P. (U.K.), S. Leeman, D.Phil., C. Metreweli, M.B., M.R.C.P. (U.K.), D.M.R.D., and K. Willson, M.Sc.

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(*Received February, 1977*)

There are various approaches to the assessment of gastric motor function. These include the use of test meals (Hunt and Spurrell, 1951), gastric multilumen catheters or pressure sensitive capsules (Eisner, 1971), measurement of the rate of drug absorption (Heading *et al.*, 1973), the passage of radioactive isotope labelled meals (Griffith *et al.*, 1966) or the appearances at barium meal examination (Kreel, 1973). Each of these techniques has its associated problems (Sheiner, 1975) and may be inappropriate to repeated or lengthy use on the same subject. There is thus a need for a non-invasive, non-radiological method of measuring gastric contractions in man.

During an investigation of the pharmacodynamics of the drug metoclopramide, a new procedure for the direct measurement of the rate of gastric contractions by ultrasound pulse-echo scanning was developed, and is described here. Although the stomach is often considered difficult to record ultrasonically, and published reports of gastric investigations have been with equipment not generally used in this country (Stein *et al.*, 1972), the technique has the advantages of being safe, non-invasive and non-trumatic. It may be employed as often as desired on both volunteers and patients alike, and it does not interfere with the action of the drugs under investigation or by itself influence gastric motility. Monitoring over long periods is possible without discomfort, and an immediate record may be obtained with scanning equipment that is now widely available in most hospitals, particularly in departments of obstetrics or radiology. For good visualization, the stomach needs to be filled with a non-gassy liquid and the presence of a solid meal makes the investigation difficult. Orange cordial at 37°C is used in our studies, the temperature appears to be important as gastric contraction waves were found to be inhibited at a lower temperature.

A standard, commercial, ultrasound B-scanner, the NE 4102 Diasonograph was used. The subject fasted overnight

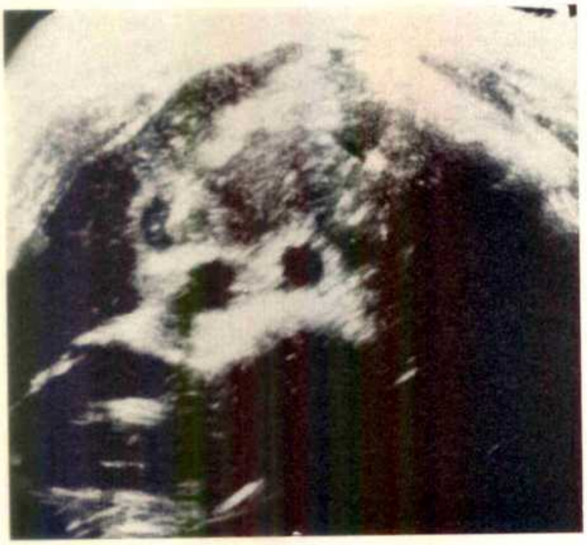

FIG. 1.

Transverse B-scan of abdomen prior to fluid meal showing echo-free transonic body of stomach.

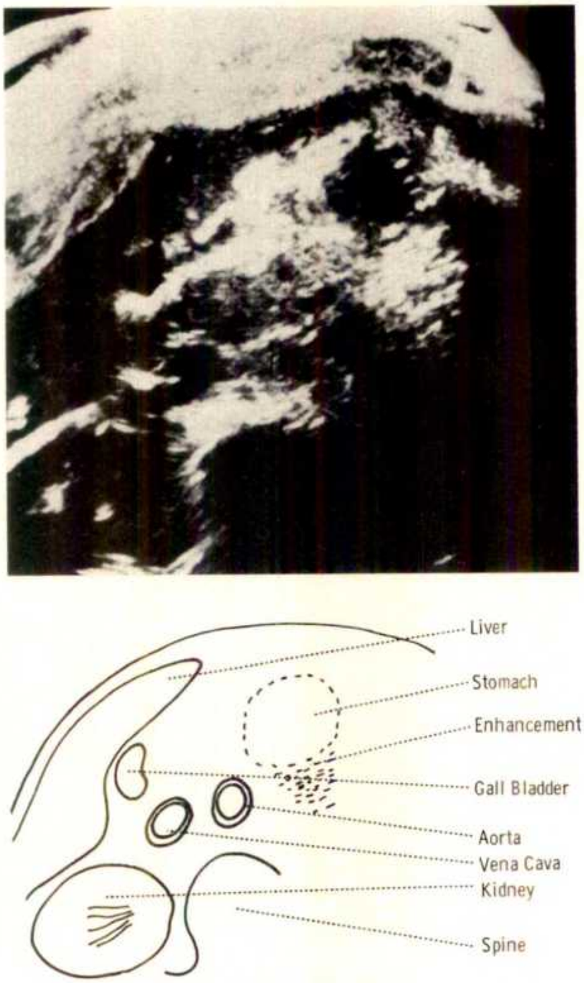

FIG. 2.

Transverse B-scan of abdomen after fluid meal showing appearance of large echo-free transonic stomach.

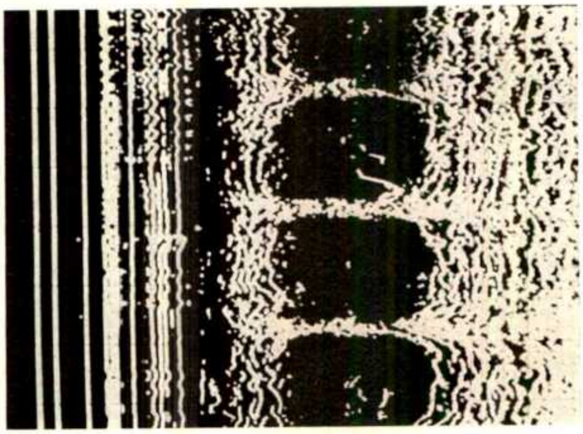

FIG. 3.
T.P. recording of gastric contractions.

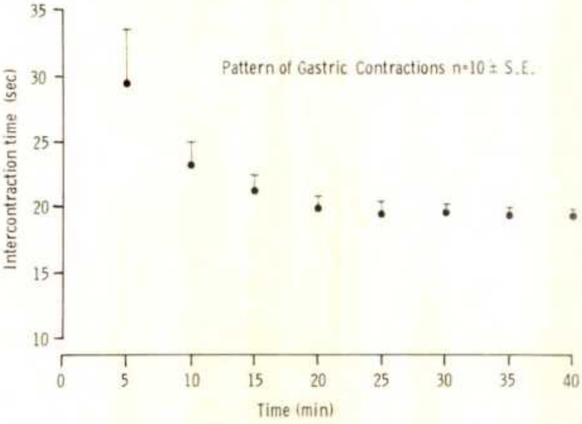

FIG. 4.
Plot of intercontraction frequency against time after commencement of meal in ten subjects.

and was seated in an upright position throughout the study. A preliminary transverse B-scan was performed at the level of the umbilicus and at a 2 and 4 cm interval both above and below this plane, using a water soluble coupling gel, at a frequency of 1.5 MHz. The transverse section of the body of the stomach could occasionally be seen at this stage (Fig. 1). Next 500 ml of liquid was inbibed, the volunteer was rescanned at the same locations, and the position of the stomach established by the appearance of an echo-free transonic region (Fig. 2). A suitable area in the antral region of the stomach was selected and the transducer locked (with a simple purpose-built device) in a direction across the displayed gastric lumen at its widest diameter, usually 1–2 cm to the left of the umbilicus. A quantitative display of the movement of the anterior and posterior walls of the antrum could then be obtained in TP- (time motion) mode, and a permanent photographic record made on Polaroid film (Fig. 3). This method is not suitable for prolonged continuous monitoring, and therefore a continuous A-mode record, up to 45 minutes duration, of the wall movement was simultaneously made directly on to video-tape. This could subsequently be replayed through the Diasonograph in either A- or TP-mode for selection of representative sections for accurate measurement. The video-tape recording facility was developed by one of the authors (KW) and is not commercially available. It could be easily built by a hospital physics department, or alternatively a commercial strip chart recorder might be used, if desired. To date 14 subjects have been investigated, and adequate recordings were obtained in all, except one case. In the normal stomach, a biphasic response to the liquid meal is seen: initially the contraction waves are slow and irregular, but after about 7–15 minutes appear more frequently, at regular 20-second intervals (Fig. 4). This rate appears to be maintained throughout the subsequent period of gastric emptying, and is easily distinguished from the more rapid, low amplitude, respiratory movements. It is of interest that the contraction waves were absent for three hours or more, after intravenous doses of 15 mg and 30 mg propantheline; the higher dose has been shown to delay gastric emptying by other workers (Nimmo *et al.*, 1973). Details of findings of pharmacological and clinical interest will be reported in the appropriate specialized journals.

The method reported here is particularly applicable to measurement of contraction rates. It is hoped to extend the technique to also enable accurate repeatable assessment of the amplitude of gastric contraction.

ACKNOWLEDGMENTS

S.L. is supported by the Wellcome Trust. The NE 4102 Diasonograph was made available by the D.H.S.S.

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

THE USE OF HYOSCINE-N-BUTYLBROMIDE (BUSCOPAN)

I fully agree with Drs. Allibone and Shaw regarding the usefulness of Buscopan for reducing intussusception in children, having used this for some years. However, I find Glucagon an even better agent, and have found that the intussusception will sometimes reduce spontaneously after Glucagon has been given.

Yours etc.,
F. STARER.

Westminster Children's Hospital,
London SW1.

REFERENCE

ALLIBONE, G. W. and SHAW, D. G., 1977. The use of hyoscine-N-butylbromide (Buscopan). *British Journal of Radiology*, *50*, 447.

THE EDITOR—SIR,

COMPUTERIZED TOMOGRAPHIC SCAN TERMINOLOGY

I followed with interest the search for a name to this new modality and wonder whether or not one can use the word computed instead of computerized. The abbreviation CT has been used and seems to be short and catchy. Perhaps TCT (Transmission Computed or Computerized Tomography) may be also put forward for consideration in view of E. R. Davies' letter in the January issue.

Yours, etc.,
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REFERENCE

RHYS-DAVIES, E., 1977. Computerized tomographic scan terminology. *British Journal of Radiology*, *50*, 77.

THE EDITOR—SIR,

WHERE SHOULD A FILM BADGE BE WORN?

When I was a registrar in England, we were told to wear our film badges under our lead aprons, at waist level.

Here in the U.S.A. film badges seem to be universally worn outside the lead apron, usually clipped to the collar. A suggestion that they should be worn under the lead apron is met with bug-eyed disbelief.

Perhaps some of your readers could tell me the best place to wear a film badge, and why.

Yours, etc.,
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Radiology Resident.

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THE EDITOR—SIR,

DIRECT REPORTING

The recent correspondence in the Journal on "Must radiologists do all the reporting" was interesting and informative. While there may be disagreement about how radiologists' time is best deployed, most people would agree that if an interpretation *is* given it should be communicated as rapidly as possible to the clinican. For the foreseeable future most radiological interpretations will continue to be typed. Reports can be made directly to a typist – "direct reporting". This is quick but very inefficient in relation to the usage of typist's time and the noise of the typewriter is disturbing to the radiologist. Reports may be recorded on audio-tape for later transcribing by an audio-typist and this is probably the most widely used system. This uses the typist's time effectively and allows the radiologist to concentrate in peace and quiet. Its great disadvantage is the inevitable time delay between recording on tape reels and subsequent transcribing by the audio-typist. A method of overcoming this problem which we have used for over a year has been of considerable interest to visitors and may interest your readers. We are using a commercially available dictation unit* which provide most of the advantages of "direct typing" without the disadvantages mentioned above. It consists of a continuous audio-tape loop (Fig.1) which enables dictating and transcribing to be done almost simultaneously. The typist can commence transcribing 12 seconds after the radiologist commences reporting and the typing station can be at some distance from the reporting area. For all practical purposes there is a continous reporting/typing process and typed reports are available for validation and signature shortly after dictation. The equipment has significantly shortened our report preparation time.

Yours etc.,
W. B. JAMES

Department of Radiology,
Southern General Hospital,
Glasgow G51 4TF.

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*Dictaphone Thought Tank System 191

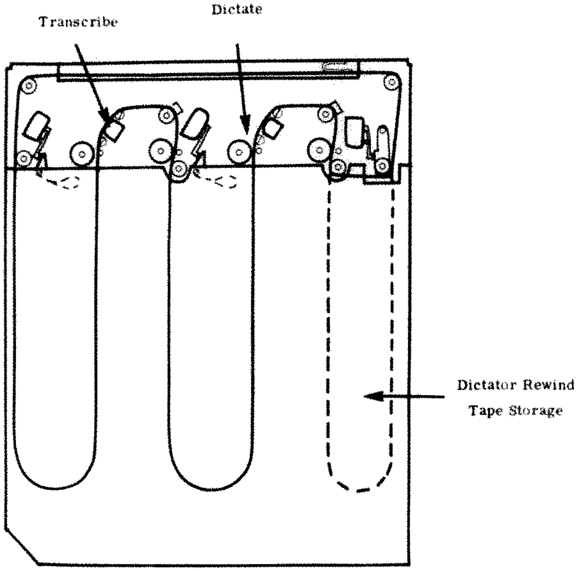

FIG. 1.

1977, *British Journal of Radiology*, *50*, 529

Correspondence

THE EDITOR—SIR,

TELEVISION FLUOROSCOPY—A NECESSITY OR AN UNSUPPORTABLE LUXURY?

The widespread acceptance by radiologists of television systems to visualize the fluoroscopic image has led, perhaps, to a less than critical evaluation of their true worth in some radiological procedures.

No experienced radiologist would dispute the essential merit of television fluoroscopy in procedures which demand complete freedom of manipulation, *e.g.* passing of catheters in angiography and other specialized procedures but its acceptance as a necessity in routine gastro-intestinal fluoroscopy may be questioned.

There is no doubt that the introduction of the intensifier tube in the 1950s resulted in a vitalizing resurgence of interest in fluoroscopy which, until that event, had undergone, over the preceding years, a continuing decline in its use. The benefits of image intensification were considerable and included a dramatic improvement in the detail visible for the radiologist and equally important, a vast saving in the radiation dosage to the patient during fluoroscopy.

An unsolved question is whether the addition of a television chain to image intensification improved either of these two important factors. Whilst readily accepting the convenience of the TV system for the radiologist, there is evidence to suggest that some inherent faults in the vidicon system have in fact detracted from the improvement in fluoroscopy which image intensification had brought. For example, radiologists who have experience in screening small plaques of calcification in coronary arteries are well aware that the movement of the heart and consequently the calcified area cannot always be accepted by the lag in the TV system and consequently the blurred image may not be visible on the television monitor.

With 2 line pairs (periods) per mm the contrast transfer of the entire TV chain is so bad as not to merit consideration and with 1 period per mm the original contrast drops to 2% of the output image (Pfeiler and Haendle, 1975). An improvement in the TV image from 625 to 1250 lines will not necessarily be the answer as at 2 periods per mm 40% of the contrast image is destroyed by noise. Furthermore, allowance must be made for the electronic deterioration of the vidicon system which inevitably occurs with time and use, and means that this system is often used well below its maximum effectiveness.

The original direct mirror viewing system introduced before the advent of TV chains was unsatisfactory, being restricted to monocular viewing and this was unacceptable to most radiologists. However, for some time now, commercial units have been available with wide-angle mirror systems which allow normal binocular viewing, but for various reasons these units have not yet achieved widespread use.

In view of the fact that the replacement cost today of a complete TV intensifier system is between £16000 and £24000 and of this the TV component is £8000 and the potential life of such a chain is about three to five years, it may be that replacement costs such as these could be an unsupportable factor in the budget of radiological departments.

One of the major manufacturers is purported to be abandoning the production of wide-angle viewers, while another is embarking on their production! It is here that radiologists should give guidance to the manufacturers who may be unconsciously lured into over-elaboration of equipment by uncritical demands from radiologists.

It has been our experience with three different makes of TV system and three direct viewing systems that for gastro-intestinal fluoroscopy the TV system has only the minimal advantage of convenience, perhaps at the expense of visible detail, over the direct viewing system. In the smaller departments where gastrointestinal fluoroscopy is only intermittently performed by a visiting radiologist, there is a distinct advantage in fluoroscopy with the wide angled mirror system as opposed to the TV system as the potentiality of breakdown is far less. Even in the larger departments, depending on the load of special investigations, the secondary back-up rooms could be planned on wide-angled mirror fluoroscopy and not on replicating the costly and expensive to maintain TV fluoroscopic units.

It is accepted that for general teaching purposes, the TV system is superior to the mirror system but the cost of replacement of the former makes it necessary that departments responsible for the training of radiologists should be prepared to train them on the mirror system as well. The radiologist trained only on the luxury of a TV system may feel frustrated if, when he attains senior status, he is expected for the first time to use a mirror viewing system for his gastro-intestinal work, whereas if previously trained in its use he will have appreciated its merits and have less prejudice in its acceptance. He will thus have the satisfaction of bringing a much needed economy to the X-ray Department without any deterioration in his standards of work.

Yours, etc.,
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T. PHILP.

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REFERENCE

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Proceedings of The British Institute of Radiology

Radioisotopes in cardiology

Abstracts of papers read at a meeting held on September 29, 1976 in the Greenwood Conference Centre, Guy's Hospital, London SE1

The Cardiac Chambers
Chairman: D. Rowlands
Quantitative methods in dynamic cardiac scintigraphy, by R. A. Shields.
Dynamic studies of left ventricular function, by N. Schad.
Abnormalities of the left ventricular wall movements, by W. E. Adam, H. Geffers, J. Sigel, F. Bitter, H. Kampmann and M. Stauch.
The assessment of left ventricular function by nuclear angiography, by A. L. Muir, W. J. Hannan, H. M. Brash, R. J. Hare, and R. E. Scorgie.
Detection and localization of cardiac shunts, by B. Pitt (*No abstract received*).
The use of single detectors in cardiac investigations, by H. J. Testa.
The evaluation of pericarditis in oncology patients by means of dual isotope scintigraphy combined with transmission scintigraphy, by P. H. Cox, A. J. Belfer and R. E. Treurniet.

Myocardium
Chairman: R. E. Steiner
Problems in the assessment of myocardial ischaemia, by E. Sowton.
Initial myocardial kinetics of ^{201}Tl in man at rest, by A. Maseri, A. Biagini, C. Michelassi, A. L'Abbate and A. Distante
Non-invasive investigations in patients with coronary artery disease, by B. Pitt (*No abstract received*).
Myocardial imaging with Thallium-201, by G. Jambroes.
Correlation of caesium scanning with electrocardiography, radiological and ultrasound data, by D. J. Rowlands and S. Walton.
Continuous assessment of regional myocardial perfusion using Krypton-81m in dogs and man; effects of nitroglycerine and stress in acute ischaemia, by A. P. Selwyn, J. P. Shillingford and J. P. Lavender.
Topographic relation between the myocardial uptake of Thallium-201 and alterations of the ventricular contour mobility in acute myocardial infarction, by T. Planiol, R. Itti and A. Pellois.
The use of Thallium-201 in the assessment and follow-up of coronary artery by-pass grafting (CABG), by R. J. Wainwright, M. N. Maisey and E. Sowton.
Myocardial perfusion scanning: a good correlation with dyskinesia, by A. H. Chapman, R. E. Steiner, M. J. Raphael and J. P. Lavender.

QUANTITATIVE METHODS IN DYNAMIC CARDIAC SCINTIGRAPHY

By R. A. Shields

Manchester Royal Infirmary

Using a gamma camera computer system it is possible to evaluate many physiologically-meaningful parameters at the same time as the visualization of form and structure. The calculation of cardiac output is described by way of the independent factors: circulation index and blood volume. Regional mean transit times and pulmonary blood volume are further parameters derived from "low frequency" tracer dilution curves (MacIntyre and Kriss, 1975). Response to high frequency fluctuations can lead to the calculation of left ventricular ejection fraction, and four methods are described for doing this through cardio-scintigraphy. (1) By producing electrocardiographically-gated end-systolic and end-diastolic blood pool images, and estimating the volumes from linear measurements (Strauss *et al.*, 1971). (2) By measuring the counts within the left ventricle at end systole and end-diastole (Parker *et al.*, 1972). (3) By measuring the extent of the fluctuations on a background-corrected high frequency dilution curve obtained from a radio-nuclide angiocardiogram (Schelbert *et al.*, 1975). (4) By determining the left ventricular counts within time-averaged images formed from the radionuclide angiocardiogram (Kurtz *et al.*, 1976). The left ventricular ejection fraction may be used to calculate end-diastolic volume, and a comparison of this with the volume obtained directly from nuclear angiographic measurements gives an index of aortic regurgitation.

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DYNAMIC STUDIES OF LEFT VENTRICULAR FUNCTION

By N. Schad

Städt Krankenhaus, Passau, Germany

Inflow of a compact bolus into the superior vena cava is essential to obtain sufficient activity and statistics during first tracer passage, so that left ventricular dynamics and wall motion after myocardial infarction can be evaluated.

The following injection technique produces a compact bolus. After puncture of an anticubital vein, 15 to 20 mCi of ^{99}Tc^{m}O$_4$ in 0.5 ml of saline are placed into a short teflon tube (capacity 0.5 ml) connected to the needle and a standard radiographic injector (Contrac 3E, Siemens). Then, a rapid injection of the tracer bolus with a saline flush of a volume of 16 ml at a flow rate of 8 ml/sec is carried out. Timing of the injection is performed so that the bolus arrives in the superior vena cava during diastole (in adults after 0.8 sec).

TABLE I

LV MAX FROM REPRESENTATIVE CYCLE

n = 70 cases—acc. int.: 50 ms—uncorrected	
Average	
	counts
	9646 (±208)
Ranges:	
in 87%	3000–13 000
in 59%	5000–11 000

TABLE II

Examinations after myocardial infarction	90
No. of patients	77
Correspondence of radioisotope major wall motion anomaly with ECG location of infarct	73
Other areas of diminished wall motion	44

With the use of a time resolution of 20 frames per second and the gamma-camera "System" 70 one can get in 89% of the cases between 700 and 2 500 counts over the left ventricle before background subtraction.

To further improve the statistic, so that wall motion of the left ventricle can be studied a representative cycle of the bolus is formed by adding six to nine sequential cardiac cycles. Thus, the first uncorrected end-diastolic image of the representative cycle reaches over the left ventricle in 87% between three to 13 000 counts (Table I). These count rates are essential as the time resolution of 50 ms is needed to obtain adequate border definition of the left ventricle and to avoid temporal blurring of the information.

In over 70 cases after proven myocardial infarction, left ventricular wall motion, regional stroke volume and ejection fraction have been evaluated and the location and extent of anomalies have been compared to the site of infarction assessed by the electrocardiogram. Marked correspondence with the site of major wall motion anomalies has been seen (Table II).

The value of the dynamic study of the left ventricle after myocardial infarction lies in the possibility of showing the dynamic result of scar formation and ischaemia, so that patients can be better graded for rehabilitation procedures. Complications can be detected early and improvement verified.

ABNORMALITIES OF LEFT VENTRICULAR WALL MOVEMENTS

By W. E. Adam, H. Geffers, H. Sigel, F. Bitter, H. Kampmann and M. Stauch

Department of Radiology, Ulm University, West Germany

With "gated blood pool methods" left ventricular wall movement may be estimated. Our procedure yields (1) amplitudes of systolic-diastolic regional contraction: akinetic regions appear as "zero amplitude" areas, hypokinetic regions reveal decreased amplitudes; (2) phases: regional time-volume-curves have similar shape within both ventricles. An aneurysm is revealed by atypical behaviour due to bulging. This can be quantitated by Fourier-analysis. The resulting phases show a marked shift within the aneurysmatic area; (3) the distribution of the regional dV/dt contraction and dV/dt relaxation in the left ventricle area; (4) ejection fraction of the left ventricle.

The reliability of the procedure was examined by (1) two subsequent investigations in the same patient under similar conditions ($n = 15$, $r = 0.93$); (2) twenty-nine patients. The results were compared with left ventriculography in RAO-position. In 27 cases full agreement concerning existence and positions of the abnormality could be registered. One small scar on the posterior wall escaped detection. One case with normal ventriculography showed abnormalities in the apex of the left ventricle (aortic valve disease).

Wall movement has been examined in 165 patients with suspected or proven coronary heart disease.

THE ASSESSMENT OF LEFT VENTRICULAR FUNCTION BY NUCLEAR ANGIOGRAPHY

By A. L. Muir, W. J. Hannan, H. M. Brash, R. J. Hare and R. E. Scorgie

Departments of Medicine and Medical Physics, Royal Infirmary, Edinburgh

In early stages of heart failure stroke volume can usually be maintained, but only by increasing the diastolic fibre length, thus a reduction in the left ventricular ejection fraction (LVEF) can be an early feature of heart failure. LVEF is widely used in assessing patients for cardiac surgery, but its measurement has relied on invasive techniques using contrast ventriculography. Nuclear angiography offers a promising non-invasive alternative, but early methods have relied on a gamma camera interfaced to a digital computer. We have developed an inexpensive alternative technique using a multi-channel analyser which allows examination of the whole ventricular volume curve. From the end-diastolic and end-systolic volume the LVEF can be computed. We have used this technique in 20 patients with ischaemic heart disease who were being considered for surgery, comparing our results with LVEF computed from contrast ventriculography and found close agreement ($r = 0.93$). In addition, as our method allows inspection of the whole volume curve, the maximum rate of systolic volume changes (dV/dt) may be calculated; this may be a more sensitive index of ventricular function. We have also compared this value with the maximum rate of systolic volume change calculated from contrast ventriculography and found good agreement.

The relative ease with which ventricular function can be measured will permit meaningful assessment of response to therapy or suitability for surgery in patients with heart failure.

THE USE OF SINGLE DETECTORS IN CARDIAC INVESTIGATIONS

By H. J. Testa

Manchester Royal Infirmary

Although in modern nuclear cardiology most procedures are now performed using sophisticated gamma camera computer systems, the basic principles of these methods were developed using single detectors. Radiocardiography was first introduced by Prinzmetal *et al.* (1948). Following his original ideas, quantitative and semi-quantitative methods were developed during the 1950s. Cardiac output and mean pulmonary transit time are derived from the classical Stewart-Hamilton equation modified for the use of an externally detected tracer. The cardiac output is obtained by dividing the count rate at equilibrium by the area under the first circulation curve ("the circulation index") and multiplying this by the blood volume. Provided that the count rate at equilibrium and the first circulation curve refer to the same blood pool, and that they are measured under the same geometrical conditions, they may be detected over any region in the body.

Mean pulmonary transit time is derived using parameters obtained from the dual-peaked praecordial curve.

Ejection fraction is calculated from high frequency curves.

Detection and quantification of intracardiac shunts and estimates of mean coronary blood flow can also be achieved, but the main use of single probe techniques is in the measurement of cardiac output, mean pulmonary transit time and left ventricular ejection fraction.

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THE EVALUATION OF PERICARDITIS IN ONCOLOGY PATIENTS BY MEANS OF DUAL ISOTOPE SCINTIGRAPHY COMBINED WITH TRANSMISSION SCINTIGRAPHY

By P. H. Cox, A. J. Belfer and R. E. Treurniet

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Rotterdamsch Radio-Therapeutisch Instituut,
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In oncology patients with pericarditis it is important to obtain maximum information concerning the condition and to what extent it is associated with malignancy. Non-invasive nuclear medical techniques can rapidly provide useful information with a minimum of discomfort for the patient.

The mediastinal shadow can be delineated by making a transmission scintigram of the thorax by means of a gamma camera and cobalt-57 flooded field source. Following this the cardiac blood pool is visualized with the aid of ^{99}Tc^{m}-labelled albumin and subsequently the myocardial muscle with ^{201}Thallous chloride injection. In this way information can be obtained concerning the presence and extent of pericardial fluid, the heart blood pool and the myocardium. ^{201}Tl has been observed to localize aspecifically in tumour tissue (Cox *et al.*, 1976) and in thoracic scintigrams good contrast can be obtained. Because of this it is possible to estimate the extent to which pericarditis is associated with malignancy involving the myocardium.

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Cox, P. H., Belfer, A. J., and Van der Pompe, W. B., 1976. Thallium 201 chloride uptake in tumours, a possible complication in heart scintigraphy. *British Journal of Radiology*, *49*, 767–768.

PROBLEMS IN THE ASSESSMENT OF MYOCARDIAL ISCHAEMIA

By E. Sowton

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The "traditional" methods of assessing left ventricular ischaemia are: (1) clinical history; (2) exercise testing; (3) atrial placing; and (4) coronary angiography. Each of them suffers from two main disadvantages: there is a large proportion of patients in whom each method gives negative results, even when the muscle is ischaemic, and there is no information concerning the site in the left ventricle which gives rise to symptoms.

It is well recognized that the severity of anginal pain bears no relation to the pathology of the coronary arteries, and examples will be shown. Even patients with normal coronary arteries may have grossly abnormal ischaemic ECG changes on exercise, and in a series of 100 patients with proven coronary artery disease only 56% stopped exercising because of chest pain.

The amount of exercise performed by this group did not differ significantly from the remainder. Only 41% of patients with clinical angina and proven coronary disease had both positive exercise and positive atrial pacing tests.

Deficiencies in functional interpretation of coronary angiographs are emphasized by the loss of demonstrable collaterals after saphenous vein grafts, and by the presence of persisting severe stenoses in symptom-free patients after graft surgery.

INITIAL MYOCARDIAL KINETICS OF ^{201}TL IN MAN AT REST

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For a more appropriate application of ^{201}Tl to the study of myocardial perfusion we investigated its myocardial kinetics in five patients with normal coronary angiograms.

A mixture of four indicators: ^{201}Tl, ^{42}K, ^{125}I RIHSA and THO (5 pts.) was injected as a bolus into the pulmonary artery. The time-concentration curves of the indicators at the aortic root and coronary sinus were obtained by a double intermittent sampling collector every 1.5 sec for 60 sec and manually every 15–120 sec up to 20–30 min.

Maximum initial extraction averaged 0.86 for both ^{201}Tl and ^{42}K relative to RIHSA. Maximal myocardial uptake was greater for ^{201}Tl than for ^{42}K because of a slower myocardial release, it occurred 10–20 min after injection and corresponded to 1.2–1.4 times the amount which was delivered to the myocardium during the first transit.

Thus measurements of total myocardial blood flow performed at time of maximal uptake would exceed by 20–40% the actual values. Myocardial scintigrams reflect the distribution of perfusion only if it remains steady during the period of faster ^{201}Tl uptake (2–4 min after injection). The early peak of ^{201}Tl uptake suggests that the initial flow dependent distribution begins to shift early to the final distribution, proportional to tissue K pool. ^{201}Tl kinetics was not apparently influenced by the level of myocardial blood flow estimated from THO curves.

MYOCARDIAL IMAGING WITH THALLIUM-201

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Scintigraphy of the heart at rest and exercise using Thallium 201 is a routine method in evaluation of coronary artery disease in our hospital.

Using six projections of the heart to evaluate all parts of the left ventricular wall it is observed that activity distribution can be inhomogeneous even in normal cases, at rest as well as during exercise. Therefore definition of the normal scintigram and interpretation of changes at exercise is rather difficult.

Although this effect is confusing and despite the fact that "cold" areas do not necessarily indicate ischaemic coronary artery disease, it is possible to delineate infarcted and temporary ischaemic areas in the myocardium with a high degree of certainty if stress-scintigrams are compared with resting ones.

In this way localization of myocardial areas at risk is easy and gross estimation of the size of infarcted areas seems possible.

Comparison of stress-ECG and stress-scintigram in a population of 60 patients with angiographic coronary artery disease showed 52% having a positive exercise ECG whereas 75% had positive stress-scintigrams.

It is concluded that although the mechanism of action of Thallium 201 is still incompletely known, cardiac scintigraphy using this radioisotope can give additional information on myocardial function and can improve reliability of stress testing significantly.

However, conclusions concerning cardiac disease cannot be based on Thallium scintigraphy alone but must be reached from careful integration of clinical and scintigraphic findings.

CORRELATION OF CAESIUM SCANNING WITH ELECTROCARDIOGRAPHIC, RADIOLOGICAL AND ULTRASOUND DATA

By D. J. Rowlands and S. Walton

Information from myocardial scanning with 2 mCi ^{129}Cs, and cardiac blood pool scanning with ^{99}Tc^{m} HSA was compared with that from chest radiography and ultrasound.

Of 44 patients with various cardiac disorders, 22 had no ECG or scan evidence of infarction, 14 definite ECG and scan evidence of infarction, four ECG disturbances obscuring possible infarction, three scan but no ECG evidence of infarction and one ECG but no scan evidence of infarction. ECG and scan localization of infarction showed general agreement and a rough correlation existed between ECG and scan estimates of infarct size.

Superimposition of the blood pool scan on the plain chest X ray was achieved using the recognizable patterns of the aortic and hilar vessels. Subsequent superimposition of the myocardial scan on the chest X ray was achieved using common markers on the technetium and caesium scans. In this way, left ventricular dilatation and hypertrophy were distinguishable.

The relationship between the short diameters of the left ventricular cavity, measured on technetium scan and by ultrasound, and that between total (cavity plus wall) short diameter of the left ventricle measured by caesium scanning and by ultrasound, were investigated. Left ventricular myocardial volume calculated by dual isotope scanning and by ultrasound showed a correlation ($r=0.81$).

CONTINUOUS ASSESSMENT OF REGIONAL MYOCARDIAL PERFUSION USING KRYPTON-81m IN DOGS AND MAN; EFFECTS OF NITROGLYCERINE AND STRESS IN ACUTE ISCHAEMIA

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The physical properties of the inert freely diffusible gas Krypton 81m (half live 13 sec) allowed the development of a technique for continuous observation and assessment of regional myocardial perfusion in dogs and man.

Krypton 81m is continuously eluted with water from a Rubidium 81 generator containing 20–30 mCi. The Krypton 81m is infused into the aortic root in physiological saline at 10 ml/min, via a Paulin ringed catheter seated below the coronary ostia. Images and simultaneous recording of count rates, from selected areas of interest are recorded continuously by a gamma camera (Toshiba GCA 202) and count rates are processed on a digital computer.

Theoretical considerations suggest that the rapid radioactive decay of this indicator relative to the myocardial turnover rate per unit mass will mean that the contribution of Krypton 81m washout to this dynamic process is small. Equilibrium of the isotope in the myocardium will principally depend on the balance between arrival of Krypton 81m and radioactive decay.

In 12 anaesthetized dogs changes in regional counts per minute using Krypton 81m were compared to changes in regional myocardial blood flow (RMBF) measured by the electromagnetic flow principle, the washout of Xenon 133 and the left atrial injection of Caesium 141 and Strontium 85 labelled microspheres. Results show a significant relationship between changes in Krypton 81m counts/min, and RMBF changes up to 200 ml/min per 100 g ($r=0.96$, $Y=0.871\times+6.77$, $P<0.001$).

In twelve anaesthetized dogs intravenous nitroglycerine caused a redistribution of regional myocardial perfusion during acute ischaemia. Perfusion in the central ischaemic, area was increased (mean difference $=+25.9\%$, $T=6.76$ $P<0.001$) and in the border zone there was a marked increase in perfusion (mean diff. $=40.5\%$, $T=16.6$, $P=<0.001$). Perfusion to the rest of the heart decreased (mean diff. $=-18.0\%$, $P<0.01$).

High resolution images and continuous monitoring of regional myocardial perfusion were recorded for up to 30 min in patients undergoing coronary angiography. Two patients showed defects of perfusion at rest which correlated with ECG and LV angiographic evidence of previous infarction. Four patients showed a normal distribution of perfusion at rest but on stress count rate analysis revealed areas supplied by diseased coronary arteries that did not increase perfusion. These areas correlated with reversible electrocardiographic changes and the appearance of chest pain. Sublingual nitroglycerine caused an increase in regional perfusion in these areas and surrounding peripheral zones.

TOPOGRAPHIC RELATION BETWEEN THE MYOCARDIAL UPTAKE OF THALLIUM-201 AND ALTERATIONS OF THE VENTRICULAR CONTOUR MOBILITY IN ACUTE MYOCARDIAL INFARCTION

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Dynamic myocardial imaging using Thallium-201 affords valuable information about the distribution of the radioactivity and the movements of the labelled structures.

Seventy-five patients from the coronary care unit have been evaluated with Thallium-201. In most cases the study was coupled with the positive labelling of ischaemic areas with ^{99}Tc^{m} pyrophosphates. Cavitary blood pool scintigraphy was systematically correlated with the myocardial examination under the same conditions.

Dynamic images are obtained in the steady state and consist of series of 16 frames describing, in a continuous way, the major part of an average cardiac cycle.

The kinetics of the cardiac cavities are analysed along the cycle by displaying superimposed isocount contours during the contraction phase on one hand and the filling phase on the other.

The complementary data obtained from the myocardial and blood pool studies provide information both on the perfusion and functional value of the myocardium and on the repercussions of coronary disease on the dynamics of the cavities.

Motion of the left ventricle and of the cardiac blood pool separately and in superimposition, in normal and pathologic cases, is presented in a film.

THE USE OF THALLIUM-201 IN THE ASSESSMENT AND FOLLOW-UP OF CORONARY ARTERY BY-PASS GRAFTING (CABG)

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The present assessment of the success of myocardial revascularization after CABG is dependent upon invasive selective contrast angiography. Thallium 201 (^{201}Tl) is an accepted potassium analogue and its distribution in the myocardium is flow-related after a simple intravenous injection. The distribution of this tracer in 20 normal subjects is described and compared with the images obtained in 13 patients on exercise before and after CABG. Prior to surgery each patient had at least one abnormal thallium image compared to 7/13 patients who had abnormal stress electrocardiograms.

At coronary angiography 34 vessels (2.6 per patient) were significantly diseased. No patient had single vessel disease. All 34 vessels were by-passed and in addition two patients had apical aneurysmectomies.

Paired t test analysis revealed a significant increase of thallium uptake in the myocardium overall ($p < 0.05$) with a highly significant increase in the territory of supply of the left anterior descending coronary artery ($p < 0.01$). One patient had premature graft occlusion two months after surgery detected by thallium scintigraphy.

It is concluded that quantitative exercise thallium scintigraphy is more sensitive than exercise electrocardiography in the detection of abnormal myocardial perfusion and is sufficiently reproducible to show changes in myocardial perfusion following coronary artery by-pass grafting allowing invaluable follow-up in a non-invasive manner.

MYOCARDIAL PERFUSION SCANNING. A GOOD CORRELATION WITH DYSKINESIA

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Myocardial perfusion scanning is a method of looking at the capillary bed of the heart. The technique has often produced apparently conflicting results, normal scans being found in association with abnormal arteriograms, and vice versa. It was with this in mind that we embarked on a study to establish what in fact the scan did show.

The scans were performed on patients undergoing routine selective coronary arteriography. ^{99}Tc^{m} human albumin microspheres were injected into each coronary artery with the patient at rest, an interval of time being allowed for coronary vasodilation to subside following the injection of contrast.

We were not surprised to find a relatively poor correlation with the ECG knowing that infarcts, especially posterior infarcts, may be missed on an ECG. The correlation with the arteriogram was better although 16% of the patients had normal scans despite critically stenosed or completely blocked vessels. We found, however, a very good correlation with dyskinesia of the left ventricle in only 4% of the patients was there no correlation.) We know that dyskinesia at rest probably represents infarction and so we concluded that the scan demonstrated infarction and nothing else. We found that abnormalities on the scan were not directly related to coronary anatomy, which explains many of the apparently conflicting results previously noted.

Biological effects of high LET radiation

Abstracts of papers presented at the Radiobiology Work-in-Progress Meeting held on Friday, January 21, 1977 at The British Institute of Radiology, 32 Welbeck Street, London W1.

Radiobiological measurements with neutrons generated by 42 MeV deuterons, by R. J. Berry, D. T. Goodhead, D. A. Bance, D. W. H. Barnes, P. Gray, R. Cox, J. Sansom and J. Thacker.
Experiments with 14 MeV and 600 MeV neutrons, by J. H. Hendry and M. Bianchi.
Differences in RBE values of 15 MeV neutrons for cells from different types of animal tumours, by J. J. Broerse, J. F. Gaiser and G. W. Barendsen.
Slow repair after X rays and fast neutrons, by S. B. Field and Shirley Hornsey.
The RBE of 15 MeV neutrons for fractionated irradiation of the rat spinal cord, by A. J. van der Kogel.
Oxygen enhancement ratio as a function of dose per fraction of fast neutrons, by Shirley Hornsey, U. Andreozzi and R. Myers.
RBE values for tumours and normal tissues for fractionated neutron irradiations, by Juliana Denekamp.
The response of two different mammalian cell types to high LET radiations, by R. Cox, J. Thacker, D. T. Goodhead and R. J. Munson.
Effects of negative pions and neutrons on the growth of *vicia faba* bean roots, by M. Bianchi, C. K. Hill, J. Baarli and A. H. Sullivan.
The effect of negative pions on the testes of the mouse, by B. E. Lambert, J. E. Coggle, and R. W. Davies.
An attempt to expand a negative pion peak to a width suitable for radiotherapy, by D. C. Lloyd.

RADIOBIOLOGICAL MEASUREMENTS WITH NEUTRONS GENERATED BY 42 MEV DEUTERONS

By R. J. Berry*, D. T. Goodhead, D. A. Bance, D. W. H. Barnes, P. Gray, R. Cox, J. Sansom and J. Thacker

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A high energy fast neutron beam potentially suitable for radiotherapy has been built at the Harwell variable energy cyclotron. Using 42 MeV deuterons on a "thin" (2 mm) beryllium target at 20μA beam current the surface dose rate 150 cm from the target was about 60 rad/minute, and 130 rad/minute with a "thick" (4 mm) target. For the former the dose-rate decreased to 50% at depths of 11.3–15.4 cm in the phantom depending on field size. The use of mainly hydrogenous materials for shielding and collimation provided beam edge definition similar to that of ^{60}Co teletherapy units, and off-axis radiation levels of about 1% which compares favourably with 14 MeV D-T generators. The biological effects of this beam have been studied in the following experimental systems: (a) clonal survival and mutation induction in Chinese hamster cells and human diploid fibroblasts after irradiation *in vitro*, (b) survival of reproductive capacity *in vivo* of murine haemopoietic colony-forming cells and murine intestinal crypts after irradiation *in vivo*, (c) survival of reproductive capacity *in vivo* after irradiation *in vitro* or *in vivo* of murine lymphocytic leukaemia cells, (d) acute intestinal death following total-body irradiation of mice and guinea-pigs, and (e) haemopoietic death following total-body irradiation of mice and guinea-pigs. The *relative biological effectiveness* of these high-energy neutrons varied from *c.* 1.0–5.0 among the different biological systems, and in several cases varied inversely with the size of the radiation dose. The *oxygen enhancement ratio* was studied in murine lymphocytic leukaemia cells irradiated under aerobic or hypoxic conditions *in vitro* and assayed for survival of reproductive capacity *in vivo*. Compared with X rays, the potential *therapeutic gain factor* for these neutrons was *c.* 1.5. This work represents a "radiobiological calibration" programme which it is suggested should be undertaken before new and unknown fast neutron spectra are used for experimental radiotherapy. The results are compared with biological studies carried out at high-energy fast neutron generators in the U.S.A.

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EXPERIMENTS WITH 14 MEV AND 600 MEV NEUTRONS

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The marked sensitivity and lack of a dose-rate effect demonstrated by bone marrow stem cells makes this population suitable for RBE studies at low dose and dose-rate. First, the main features of the radiation response of this population are outlined with respect to survival curve shape, dose-rate and split-dose effects. The lack of a dose-rate effect (down to 3 rad/h) over the first decade of depopulation is compatible with the marked initial slope of the survival curve, if the latter is explained in terms of single-hit lethal damage.

Survival measurements using the spleen colony assay, for neutrons at 25 rad/h produced by 600 MeV protons on Be, showed an RBE value of 1 for up to 50 rad of neutrons (with reference to γ-rays at 40 rad/h). The RBE then increased with dose, and at 10% survival it varied between 2.0 for the left femur which was towards incident beam to 1.4 for the right femur which was away from incident beam (in initial dose build-up region). This unexpected curvature is discussed in relation to similar measurements for 14 MeV D-T neutrons, which are continuing.

DIFFERENCES IN RBE VALUES OF 15 MEV NEUTRONS FOR CELLS FROM DIFFERENT TYPES OF ANIMAL TUMOURS

By J. J. Broerse, J. F. Gaiser and G. W. Barendsen

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Impairment of the clonogenic capacity of cells has been measured as a function of the dose of 300 kV X rays or 15 MeV neutrons for nine different cell lines in culture. These cell cultures were derived from various types of tumours in rats and mice, including carcinomas, sarcomas and a lymphoma.

The survival curves obtained for different cell lines show a large variation in sensitivity. Largest and smallest doses required to cause 50%, 10% and 1% survival differ by factors of 4.6, 3.4 and 3.2 respectively for X rays, and by factors of 3.5, 3.0 and 2.9 respectively for 15 MeV neutrons. RBE values of 15 MeV neutrons range from 1.8 to 3.3 for the 50% survival level, but are much more similar at lower percentages survival. Implications of these differences in intrinsic cellular radiosensitivity for fast neutron radiotherapy were discussed.

SLOW REPAIR AFTER X RAYS AND FAST NEUTRONS

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The LD_{50} between 40 and 180 days after irradiation of the thorax of mice has been used as an index of radiation damage to the lung. The target cells are not known for certain, but may be either capillary endothelial cells or the type II alveolar epithelial cells which are responsible for production of alveolar surfactant. Both cell types are known to proliferate slowly.

Previous observations (Field *et al.*, 1976) have indicated a slow repair process after irradiation with X rays, with a half time of about 100 hours (in contrast with the half time of one or two hours for Elkind type repair of sublethal damage). Experiments to investigate slow repair in the lung were repeated using a different strain of mouse and giving two fractions of X rays or fast neutrons separated by times of one hour up to five weeks. As was found in the earlier work, there was slow repair after X rays, but with neutrons, there was no further repair after one hour (this latter is probably due to repair of sublethal damage).

If this result were general, and not specific to the particular system used in these experiments, it would mean that the RBE for neutrons would increase as the overall time were increased. The result also implies that retreatment after neutrons would be more hazardous than after X rays.

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THE RBE OF 15 MEV NEUTRONS FOR FRACTIONATED IRRADIATION OF THE RAT SPINAL CORD

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In a number of clinical trials with fast neutrons, head and neck tumours are irradiated. For these treatments, brain and spinal cord are important dose limiting normal tissues. The RBE-values derived for the tolerance of the spinal cord with single doses and five fractions have been reported to be in the same range as for tolerance of various other normal tissues (Van der Kogel and Barendsen, 1974). However, extrapolation from these experimentally derived RBE values to a clinical dose range of 80–100 rad per fraction might lead to serious errors.

Three-month-old male WAG/Rij rats were irradiated on the vertebral region L2–L5 with collimated beams (diameter 25 mm) of 15 MeV neutrons. Average daily doses $(n+\gamma)$ of 86.5 rad were given in a varying number of fractions, up to 2500 rad in 29 fractions. The tolerance dose, at which less than 10% of the rats develop paralysis, was estimated to be 1850–1900 rad. It is shown that no significant increase in tolerance is obtained when the neutron dose to the spinal cord is administered in 23 fractions instead of in five fractions. In contrast to this observation for neutrons, the tolerance dose for X rays shows a strong increase with decreasing dose per fraction. Consequently, a relatively high RBE value is obtained at low dose per fraction. In the present experiments, the RBE is 3.6 at a dose of 86.5 rad per fraction. These results indicate that, while early skin damage might be prevented by decreasing the dose per fraction, a certain total dose should not be exceeded because of a considerable risk of severe late normal tissue damage.

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OXYGEN ENHANCEMENT RATIO AS A FUNCTION OF DOSE PER FRACTION OF FAST NEUTRONS

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The amount of sublethal damage deposited by neutron irradiations varies from one tissue to another. This is demonstrated by differences in (D_2-D_1) which measures the recovery from this sublethal damage. (D_2-D_1) values for neutrons from the Hammersmith cyclotron beam vary from 0–15 rad for the haemopoietic stem cells, 100–200 rad for lung damage (Field and Hornsey, 1974) to ~350 rad for necrosis in mouse tails (Hornsey *et al.*, 1977). However, even for damage showing large (D_2-D_1) values such as radiation pneumonitis and tail necrosis, there is very little further sparing of damage by more fractionation of neutron dose (Hornsey *et al.*, 1975; Hendry *et al.*, 1976). It has been suggested that this is due to the higher relative contribution to damage at low doses or doses/fraction from the high LET components of the radiation, in particular the α particle and heavy recoil nuclei produced by neutron interactions. If this were the case, the OER should decrease as the proportional contribution to damage from the high LET component increases, *i.e.* the OER should decrease as the number of fractions is increased and the dose/fraction of neutrons is decreased (Hornsey *et al.*, 1977). Using early (at 15–45 days post-irradiation) and late (45–90 days) skin reactions in mouse tails as the measure of radiation damage after neutron irradiations of normal tails in air or oxygen, or occluded tails in N_2, the OER fell from 1.4 for single doses to 1.1 for ten fractions.

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RBE VALUES FOR TUMOURS AND NORMAL TISSUES FOR FRACTIONATED NEUTRON IRRADIATIONS

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The RBE for fast neutrons has been shown by Field and Hornsey (1971) to vary with the dose per fraction for various normal tissues. The exact value for each normal tissue depends on the change in D_0 and D_q for neutrons relative to X rays for the constituent tissue cells.

For single dose experiments on tumours, most of which are limited to large doses per fraction, the RBE is higher than for the normal tissues because of the hypoxic radioresistance to X rays of some tumour cells. This results in a therapeutic advantage from using fast neutrons (*i.e.* more tumour damage without increasing the normal tissue damage).

When fractionated treatments are used, reoxygenation may occur between the successive fractions, which would lower the advantage of fast neutrons. For the five different tumours which have been studied, of widely differing histology and growth rates, the RBE for the tumour falls within the range for skin when small doses per fraction are used. This indicates that the therapeutic gain is indeed lost at low dose fractions.

In one tumour, Ca.NT, the persistence of hypoxic cells has been demonstrated by sensitization of the tumours to fractionated neutrons even at 200 rad per fraction. It is suggested that the loss of therapeutic advantage may result from a greater change in the repair capacity of normal tissues than of tumour counterbalancing the improvement due to better eradication of hypoxic cells.

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THE RESPONSE OF TWO DIFFERENT MAMMALIAN CELL TYPES TO HIGH LET RADIATIONS

By R. Cox, J. Thacker, D. T. Goodhead and R. J. Munson

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Inactivation and mutation of two mammalian cell types (Thacker and Cox, 1975) were measured after irradiation with helium, boron and nitrogen ions of LET in the range 20–470 keV μm^{-1}. Cultures of freshly-isolated human fibroblasts and established Chinese hamster V79 cells gave similar forms of RBE–LET relationship for both inactivation and mutation, with RBE maxima in the LET range 85–200 keV μm^{-1}. The relationship for inactivation broadly resembled that previously published for cultured mammalian cells (*e.g.*, Barendsen, 1968). Unique RBE values could not be given for the hamster cells since the plots of the logarithm of surviving fraction and the induced mutation frequency against dose were curvilinear at low LET. However, for all radiations these quantities were linearly related to dose for the human cells and the RBE maxima were four for inactivation and seven for mutation induction.

Small differences in the form of the RBE–LET relationship for the inactivation of human and hamster cells may be correlated with differences in the abilities of the two cell types to recover from low LET (including δ ray) damage, although other explanations cannot be excluded.

Preliminary karyotypic analyses of human cells suggest that specific chromosome aberrations are present in mutants induced by high LET radiation. This observation may explain the higher maximum RBE for mutation relative to inactivation, since such aberrations have not yet been found in mutants induced by low LET radiation.

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EFFECTS OF NEGATIVE PIONS AND NEUTRONS ON THE GROWTH OF *VICIA FABA* BEAN ROOTS

By M. Bianchi, C. K. Hill, J. Baarli and A. H. Sullivan

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Vicia faba bean roots have been irradiated with neutrons of various energies and with negative π-mesons and the effect on the ten day growth of the roots determined. The neutron irradiations were made in beams of 400 and 600 MeV maximum neutron energy, as well as neutrons from a plutonium–beryllium source (mean energy 4.4 MeV) and from a 14-MeV neutron generator. The bean roots have also been irradiated at various points along the depth-dose curve of negative pions coming to rest, including the region where the pions stop and annihilate in interactions with nuclei. Induction of micro-nuclei was also investigated in the bean roots irradiated with pions.

The RBE determined from these measurements were reported as well as discussion of the RBE dependence on dose and radiation quality.

THE EFFECT OF NEGATIVE PIONS ON THE TESTES OF THE MOUSE

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The effect of 70 MeV negative pions on the survival of mouse spermatogonial cells and on testis weight loss is reported. The Rutherford High Energy Laboratory pion beam was used in two cell survival experiments; one measuring the death of late type A/intermediate spermatogonia and the other measuring type B spermatogonia. Both these experiments were performed in SAS/4 mice breathing either air or 10% oxygen. Comparative experiments were performed using 200 kV X rays.

The RBE for pions (compared with X rays) for spermatogonial survival was about 1.5. An oxygen enhancement ratio (OER) of 1 was obtained for pion irradiation of spermatogonia. At present, the RBE value for pions for testis weight loss seems to be not very different from 1.

AN ATTEMPT TO EXPAND A NEGATIVE PION PEAK TO A WIDTH SUITABLE FOR RADIOTHERAPY

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π-meson beams having a single momentum produce a depth profile with a peak which is too narrow for radiotherapy. Previously published work (Lloyd *et al.*, 1975) with the Rutherford Laboratory's beam at 160 MeV/c gave a peak 14 cm deep in water and with a peak to plateau ratio of biological damage 1.7 times the dose ratio. However, the peak had a width at half-height above the plateau of only 3 cm.

An experiment is described in which an expanded peak was produced by the superposition of three pion momenta (128, 146 and 166 MeV/c). Assuming a biological enhancement factor of 1.7 for each, the three momenta were combined in the ratios 0.27, 0.46, 1.0 to produce a peak having a width at half-height of ~10 cm and being approximately flat-topped. This was compared with experimental observations in which the yield of dicentric aberrations was measured in human blood samples irradiated at various depths in a water phantom. The chromosome damage profile produced an expanded peak ~7 cm wide and the main departure from the expected shape was a steeper fall off at the position corresponding to the peak of the highest momentum. It was shown that at 166 MeV/c an enhancement factor of 1.2 was more appropriate.

It is concluded that this approach to peak widening is feasible but further attempts should be preceded by a more detailed study of likely momenta, examined separately, to determine the relationship between dose and biological effect at varying depths especially across the peaks.

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Obituary

Professor P. K. Halder

Professor P. K. Halder, 1915–1976, was well known and widely respected internationally as an eminent radiotherapist and as one of the founders of modern radiotherapy in India. He was born in Uttar Pradesh in 1915 and was trained in medicine in King George's Medical College, Lucknow. Training first in surgery, he changed to radiotherapy and was a student in the U.K. in 1947, later returning to the Medical College, Agra, to the All India Institute of Medical Sciences, Delhi and finally to the J.K. Institute of Cancer Research in Kanpur. Professor Halder was respected by all for his wisdom, wide vision and creative ability and was one of the founders of modern radiotherapy in India and a leader in the development of cancer education and the organization of cancer treatment. He was eminently a clinician and a teacher and played an important part in the establishment of the Indian College of Radiology of which he was a founder chairman. He was the author of numerous papers on the treatment of cancer and was responsible for the design of an applicator used widely for treatment of cancer of the cervix. He was a past chairman of the Indian Radiological Association and chairman of many committees.

Professor Halder had many friends in the U.K. where he was awarded in 1976 the Fellowship of the Royal College of Radiologists and will long be remembered with affection together with Mrs. Halder and their daughters—not only for his wisdom as a radiotherapist and a teacher but also for his appreciation and knowledge of the history and arts of India, to which they introduced many overseas guests.

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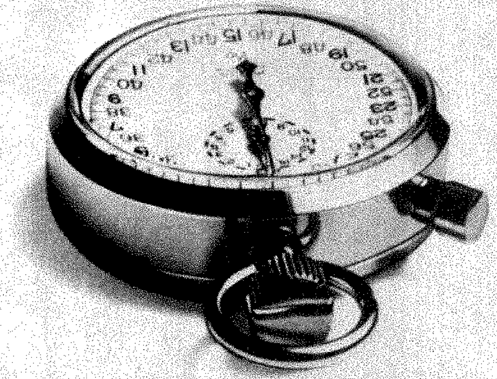

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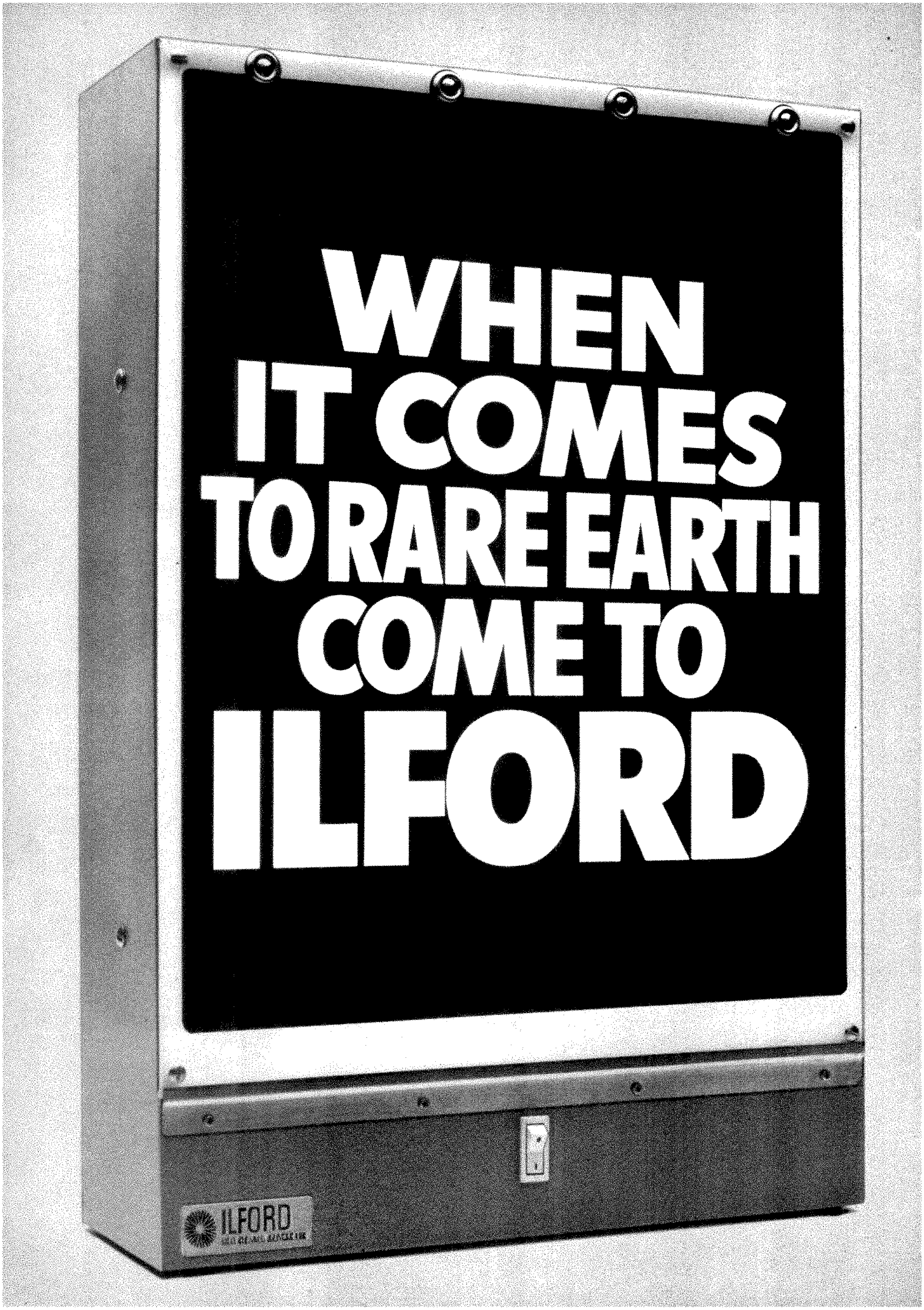
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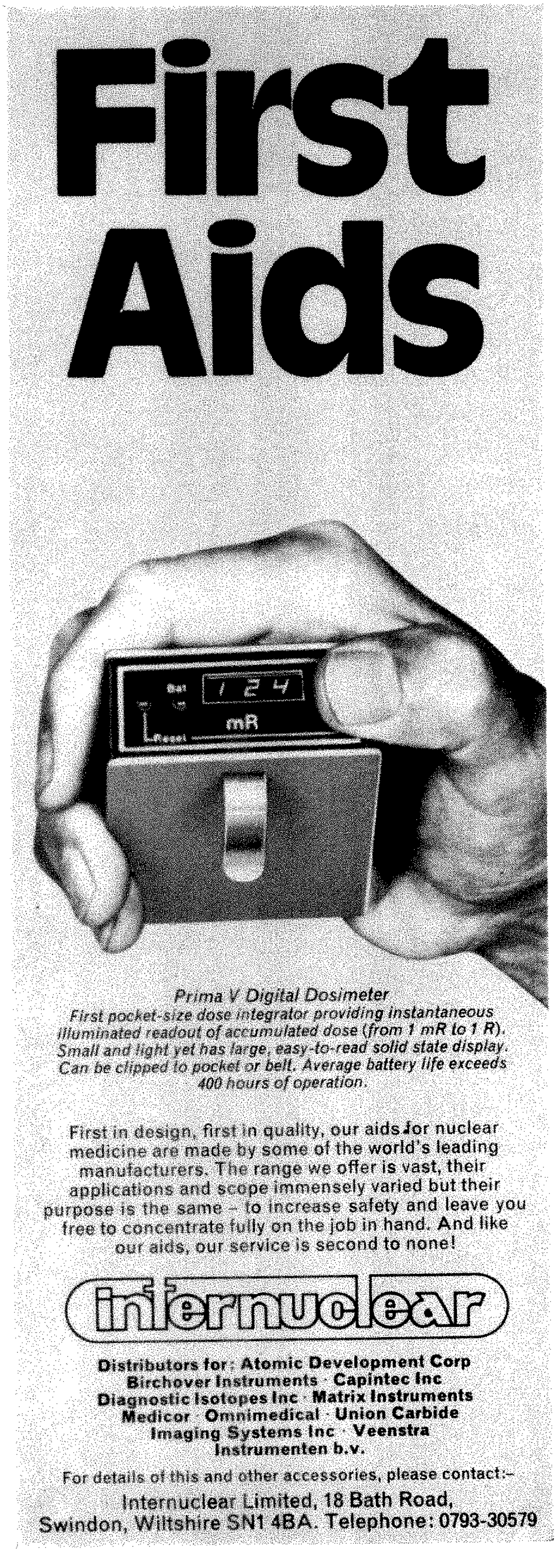

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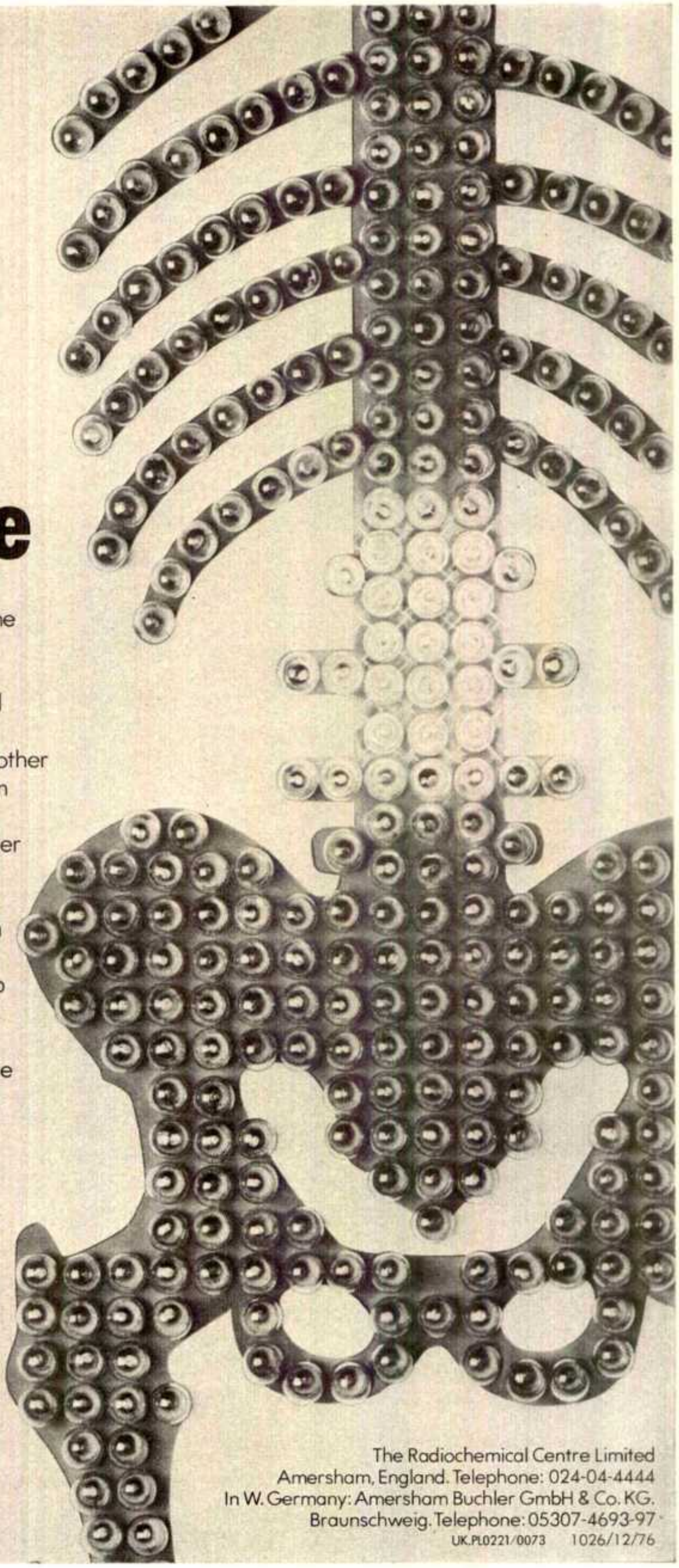

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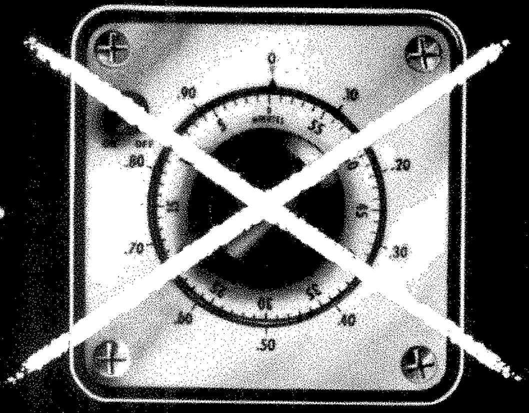

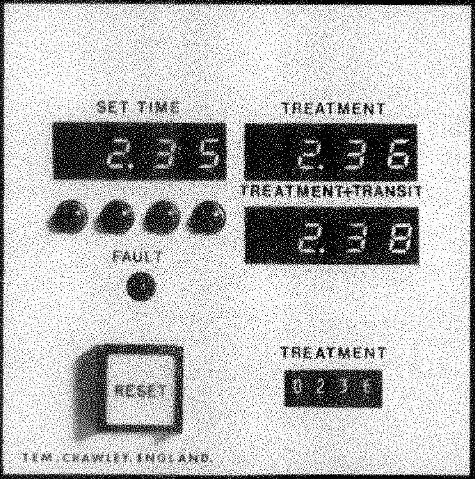

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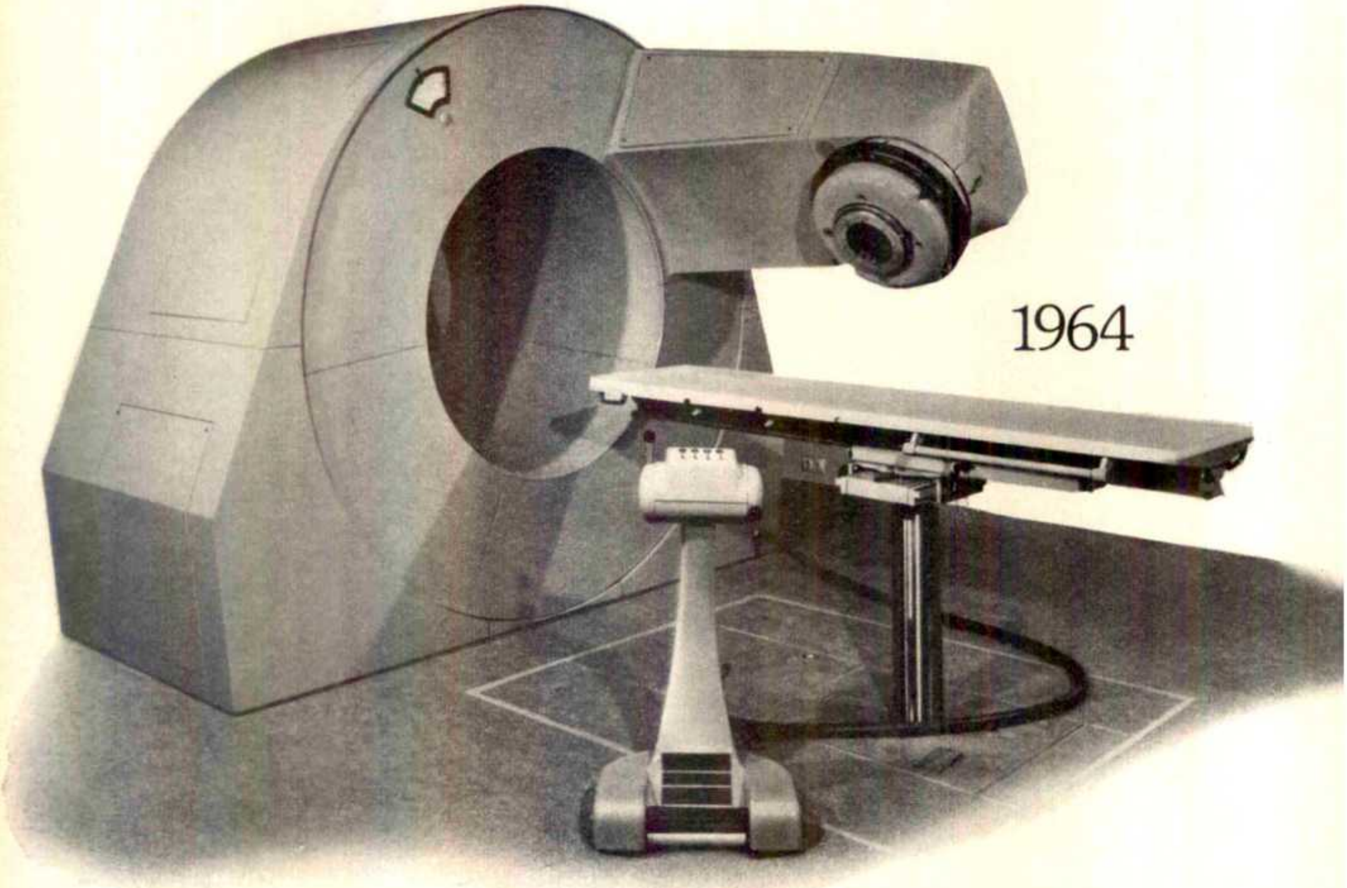

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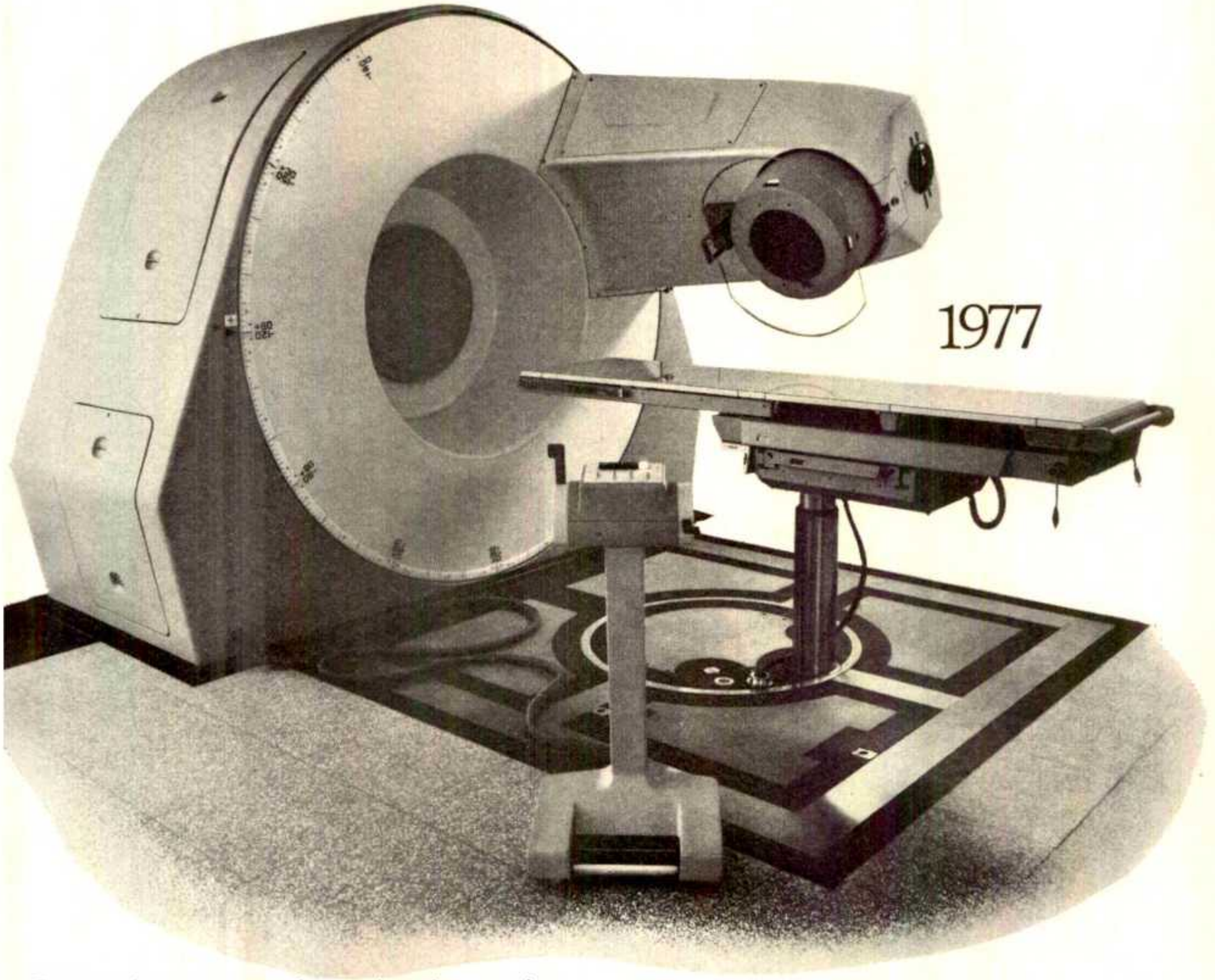

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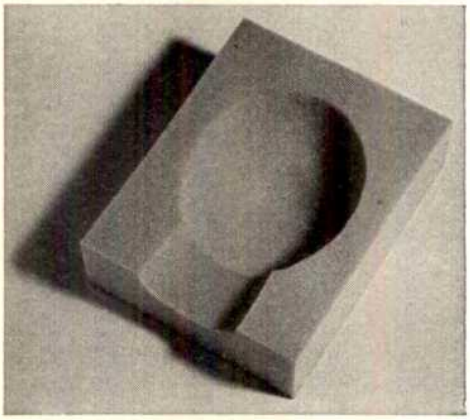

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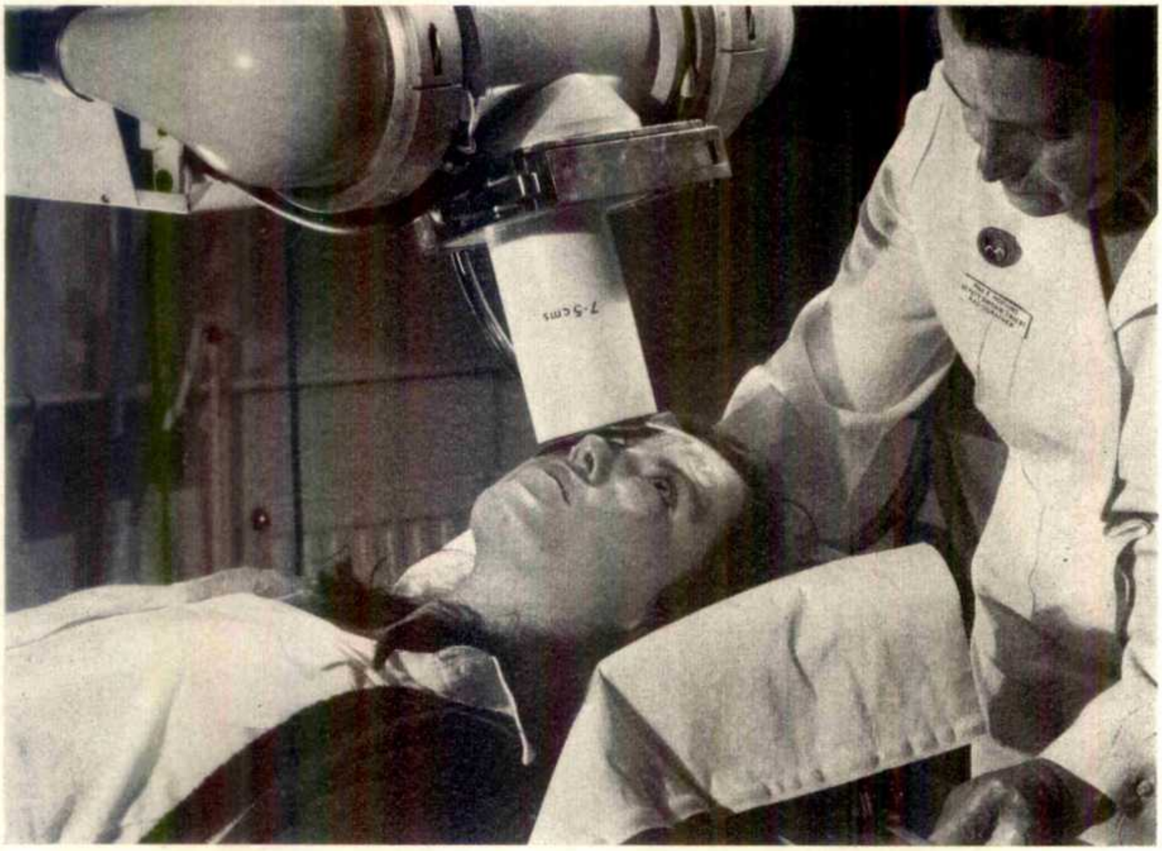

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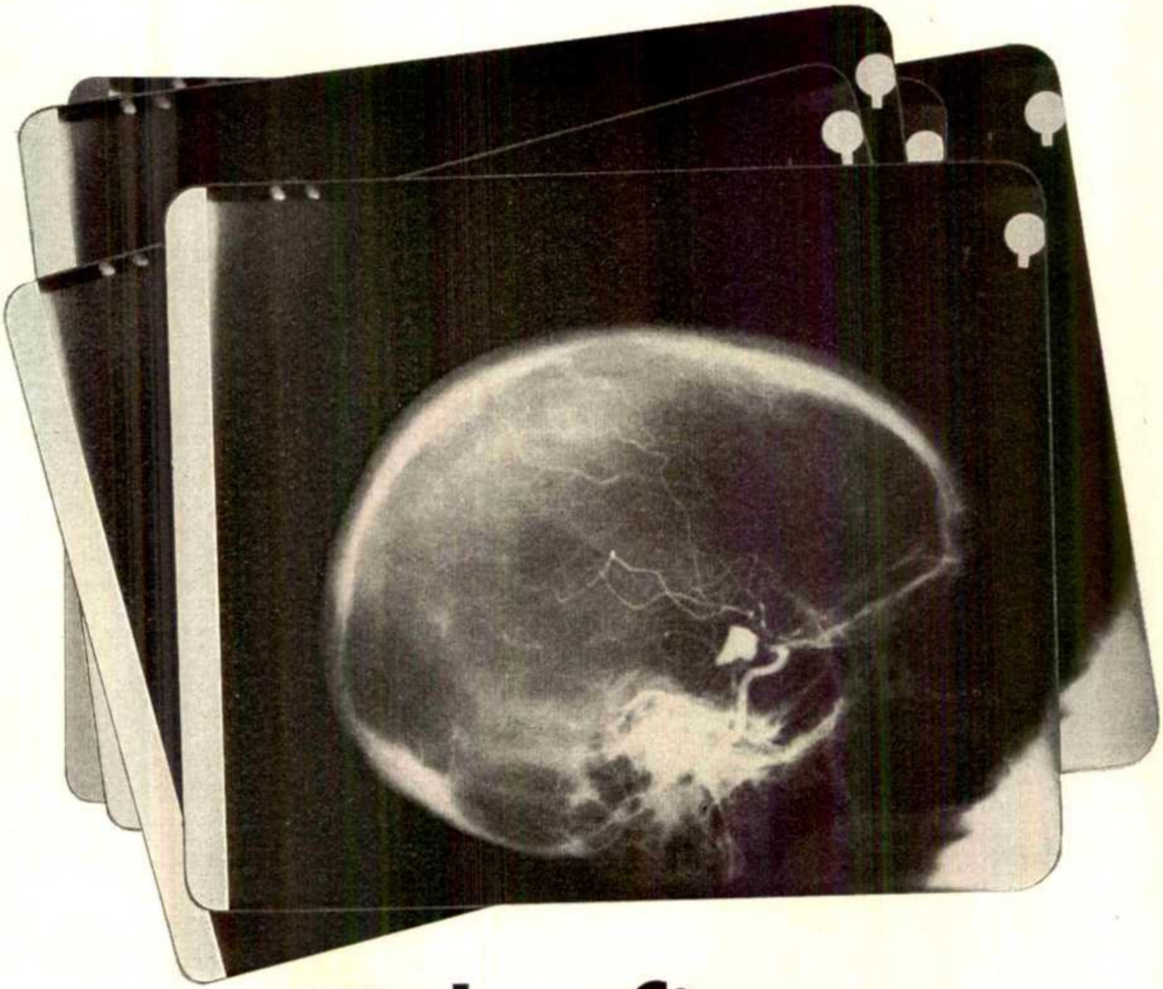

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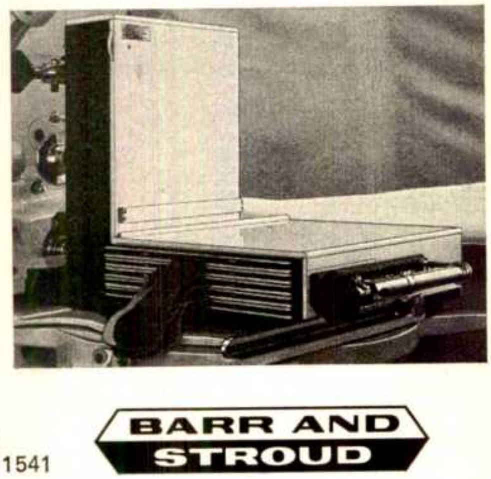

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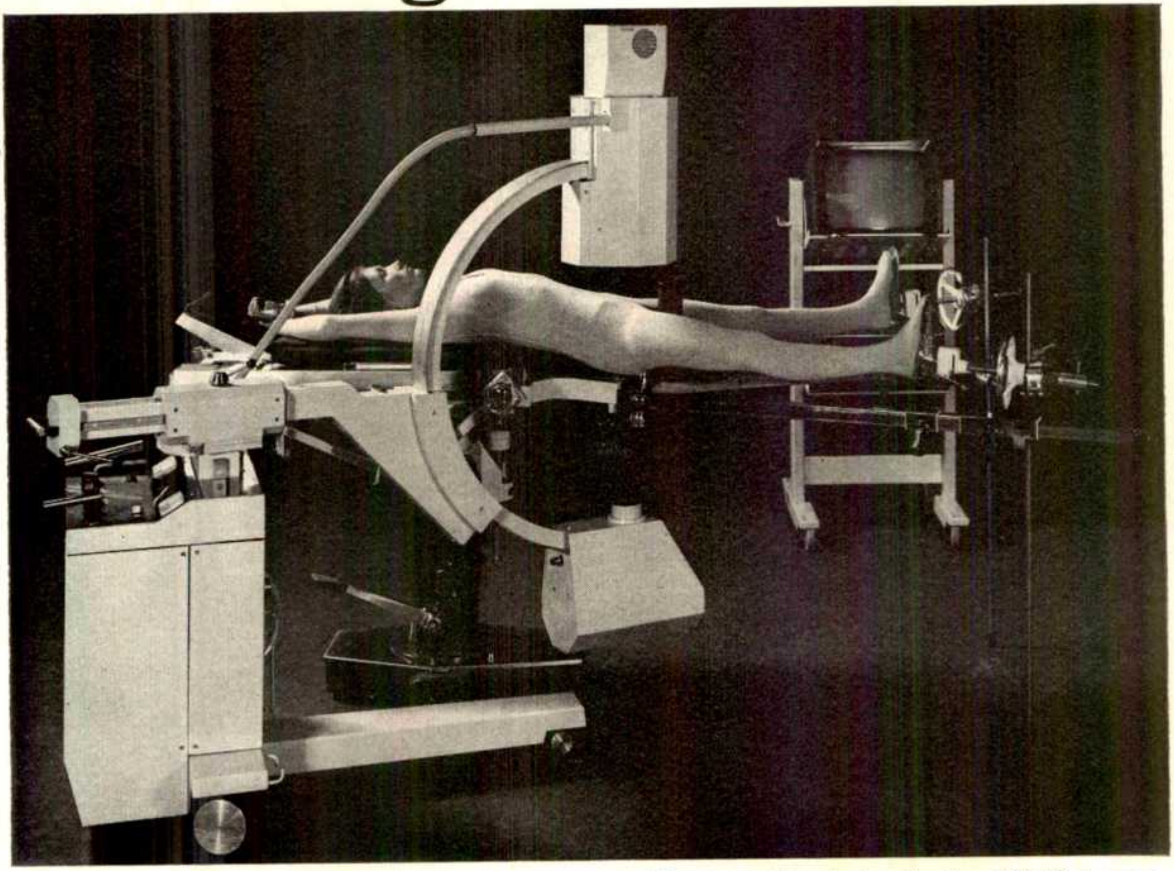

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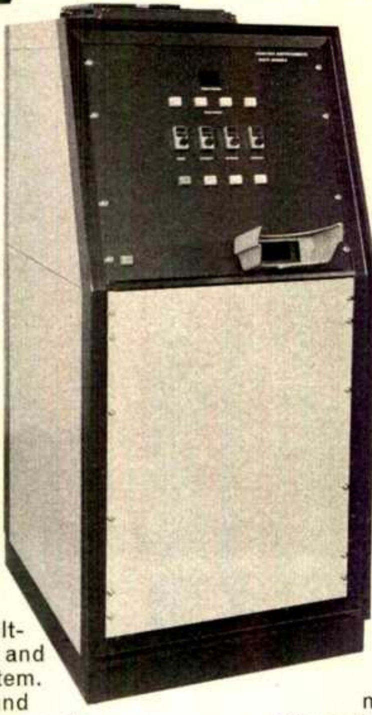

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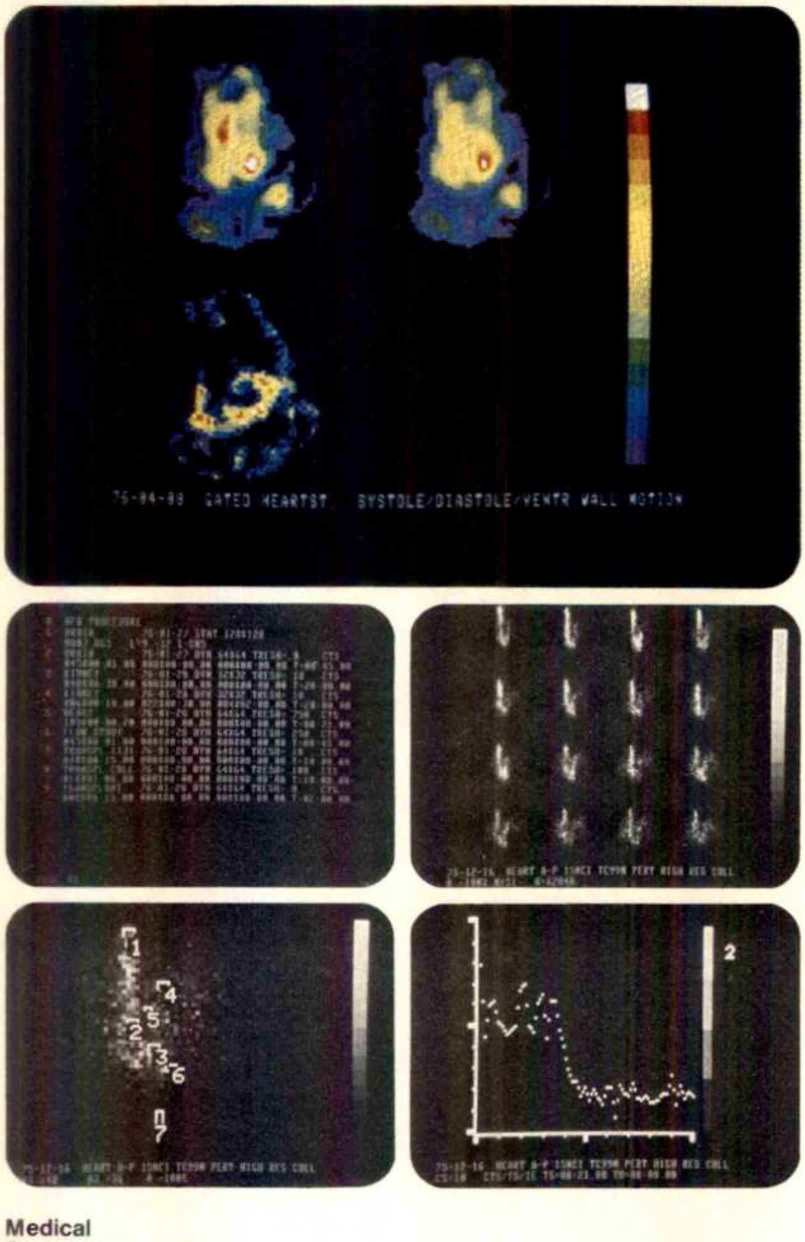

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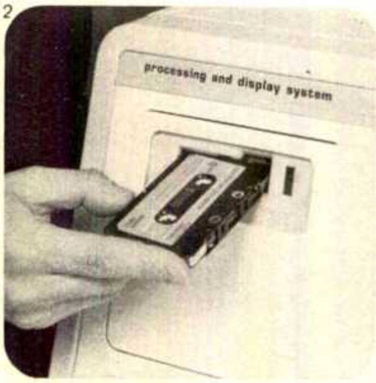

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The British Journal of Radiology

Radiology now

Wide ureters, a dilemma in diagnosis*

The presence of an abnormally wide ureter, or ureters, on an intravenous urogram is a fairly common finding in any radiology department. All too often it is implied that such dilatation must be due to some form of obstruction, and this unfortunate misinterpretation may lead to a needless or incorrect operation. The ureter is a distensible muscular tube whose function is to propel urine from the kidneys to the bladder. It responds to an increased fluid load by an increase in its peristaltic activity and, if the load is great enough, by compensatory hypertrophy, and then dilatation. This type of dilatation is observed in diabetes insipidus, where the urine output may approach 20 litres per day. A much commoner example of dilatation due to an increased fluid load is seen with vesico-ureteric reflux, particularly in children, where it can produce marked widening of the ureters with or without associated calyceal abnormality. Frequently such reflux is related to a primary defect at the vesico-ureteric junction—a short, horizontal course of the intramural ureter being the usual explanation. Less commonly, reflux occurs secondary to a neuropathic bladder or to bladder outflow obstruction. The former requires a careful scrutiny of the spine, and the patient's back, for the occult forms of defect, and the latter a micturating cystogram for a complete examination of the urethra. This is particularly important in male children if urethral valves are not to be missed.

If cysto-urethrography excludes reflux and reveals a normal bladder and urethra, does this imply that the widened upper tract is dilated secondary to obstruction at the uretero-vesical junction? Although many people might still reply in the affirmative, this assumption is not necessarily correct. The concept of the "non-obstructed, non-refluxing wide ureter" is not new (Shopfner, 1966). It implies that ureters may be wide because they are intrinsically abnormal. The primary defect, either congenital or acquired, lies in the wall of the ureter. The dysmorphic systems with defective musculature seen in the Prune Belly Syndrome and in ectopic ureters associated with renal dysplasia provide evidence of such a congenital intrinsic defect. Dilated and distensible ureters, particularly on the right, are sometimes seen in the adult parous female. A combination of hormonal effect and past or present urinary tract infection has been postulated (Spiro and Fry, 1970; Guyer and Delany, 1974). In any event, there is no evidence of obstruction, and reflux cannot be demonstrated. There is experimental evidence that infection alone can produce ureteric dilatation (Jeffs and Allen, 1962) and some circumstantial evidence in children (Shopfner, 1966). It has been reasonably postulated that some ureteric dilatation may represent the aftermath of previous reflux, with or without infection, which has spontaneously ceased (Hutch and Tanagho, 1965).

What about the 'primary "megaureter"? Confusion still exists as to the nature of this condition—seen both in children and adults—and several classifications have been suggested (Belman, 1974; Whitaker and Johnston, 1976; Glassberg, 1977). The benign course of so many, particularly in the adult age group, and the controversy about their management is concerning (Wiliam and Hulme-Moir, 1970; Heal, 1973). Further interest in the nature of this abnormality has been provoked by perfusion techniques, previously used in the experimental animal (Backlund and Reuterskiold, 1969), and recently introduced as a clinical tool (Whitaker, 1973). After percutaneous renal puncture, the system is perfused and the pressure differential between the upper tract and bladder is measured at different flow rates. Current evidence suggests that many non-refluxing dilated systems are not obstructed, and implies that re-constructive surgery is not indicated.

Is the radiologist able to establish whether obstruction exists? In acute obstruction an immediate persistent and increasingly dense nephrogram is invaluable in establishing a diagnosis at urography. Such nephrographic appearances are not seen in chronic obstruction. Delay in pelvicalyceal opacification and in the passage of contrast medium through the ureter occurs both in the dilated system which is obstructed, and also in the one with simple stasis, and cannot be used as reliable evidence of obstruction. Delay in passage of contrast medium across the uretero-vesical junction does not necessarily imply that the patient's primary abnormality lies at that level. Ureters have difficulty in emptying satisfactorily into a high pressure bladder, such as is seen with outflow obstruction—a functional obstruction exists, and a variable degree of ureteric dilatation ensues. In such cases, the clue, on the urogram, to the presence of outflow obstruction, whether valves in children or an enlarged prostrate in adults, is the appearance of the bladder, which is often large or trabeculated and usually exhibits a significant post-micturition residue. Once the outflow obstruction has been dealt with, the functional obstruction at the uretero-vesical junction is usually relieved, although the ureteric dilation frequently persists to a variable extent.

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*Reprints from: Dr. C. D. R. Flower, Radiology Department, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ.

Following urography, there will remain a group of patients with dilated upper tracts where both clinician and radiologist remain in doubt. Retrograde studies provide little more than a demonstration of morphology, and do not allow an appraisal of the dynamic situation. Radioisotope renography, which provides a semi-quantitative estimate of renal function, often does little more than the urogram in establishing whether there is poor drainage from the kidneys. It, too, cannot always distinguish between stasis and obstruction, and its greatest value is in the performance of serial studies. There is an increasing use of quantitative imaging techniques using radiopharmaceuticals such as $^{99}Tc^m$ DTPA, and it is possible that they will aid in this differentiation. However, it is difficult to be convinced of this at present.

In summary, it is of fundamental importance to realize that not all dilated ureters are obstructed, and that the radiologist's inability to demonstrate reflux up a dilated ureter should not mislead him into suggesting, *ipso facto*, that it is obstructed. When faced with the non-refluxing dilated system, the decision to operate should rest upon the definite likelihood of improvement. This usually implies providing objective evidence of obstruction at the uretero-vesical junction. Conventional radiographic methods have definite limitations in this regard. Perfusion techniques require skill in antegrade pyelography, specialized equipment, and a keen rapport between the various clinical specialities. Such pressure/flow studies offer the most accurate means of diagnosing ureteric obstruction, and interested radiologists should familiarize themselves with this field if they hope to offer a more rational diagnosis when posed with the problem of the wide ureter.

C. D. R. Flower

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In vivo and *in vitro* assessment of barium sulphate suspensions*

By G. M. Roberts, M.R.C.P., F.R.C.R., E. E. Roberts, D.S.R., R. Ll. Davies and K. T. Evans, F.R.C.P., F.R.C.R.

Department of Diagnostic Radiology, Welsh National School of Medicine, Heath Park, Cardiff

(*Received July, 1976 and in revised form February, 1977*)

ABSTRACT

In vitro methods of testing the efficiency of barium sulphate suspensions in delineating mucosal detail using canine cadaveric stomachs have been described in the literature. In this study a comparison is made between *in vitro* and *in vivo* tests in the stomach and small intestine of dogs, using several brands of barium sulphate. The results indicate that there is considerable variation in the behaviour of these suspensions between the *in vitro* and *in vivo* tests particularly in the stomach. It is our view that *in vitro* tests of this sort are of little value for assessing the relative advantages and disadvantages of these suspensions in demonstrating mucosal detail.

Double contrast radiography of the stomach has been introduced in order to demonstrate fine mucosal detail and small mucosal lesions (Shirakabe 1971; Kreel *et al.*, 1973). In order to assess the ability of barium sulphate suspensions in coating the mucosa evenly and thinly to outline such fine detail, stomachs from animals, human cadavers and operative specimens have been radiographed following the application of barium sulphate suspensions to the mucosal surface. The relative advantages and disadvantages of various suspensions have been enumerated on the basis of *in vitro* testing (Kreel *et al.*, 1974; Kreel, 1975a; Kreel 1975b).

In the present study a number of barium sulphate suspensions were tested in living and cadaveric dog stomachs and small intestines. The study was prompted by the finding that one barium sulphate suspension tested in this way in a preliminary study gave very different results depending on whether the experiments were carried out *in vivo* or *in vitro*. There were also discrepancies between the behaviour of the same barium in the stomach and in the small intestine of the same animal. This observation also led to a separate study of some factors affecting the behaviour of barium sulphate suspensions in gastric secretion (Roberts *et al.*, 1977).

MATERIALS AND METHODS

In vivo studies on the stomach and small intestine were carried out on eight mongrel dogs weighing 12–20 kg. A total number of 77 cadaveric specimens were used for the *in vitro* tests—23 stomachs and 54 lengths of jejunum.

In vivo *examination of the stomach and small intestine*

Solid food was withheld on the morning of the examination, but the dogs were not deprived of water. They were anaesthetized using intravenous Pentothal (25 mgm/kg body weight) and the stomach or duodenum, depending on the organ to be studied, was intubated. Sixty ml of the barium sulphate suspension to be tested were introduced. For examination of the stomach an anticholinergic agent (Probanthine 15 mg intravenously) was administered and up to 400 ml of air was introduced under fluoroscopic control. Following repeated rotation of the animal to assist coating of the mucosa, the stomach was radiographed in the antero-posterior and both oblique projections. For the small intestinal studies barium was allowed to reach the mid small intestine, when it was paralysed in the same way as the stomach and inflated with air under fluoroscopic control. Oblique radiographs of the abdomen were taken.

In vitro *examination of the stomach and small intestine*

Cannulae were introduced into both ends of freshly removed specimens and the mucosa was

TABLE I

THE STOMACH—SCORING FOR MUCOSA

Barium preparation	*In vitro*		*In vivo*	
	Detail	Coating	Detail	Coating
Micropaque	3	3	0	2–3*
Baritop	0–3*	0–2*	0	0–1*
Liquibarine	0–1*	1–2*	0	2
High density preparation	0–3*	0–2*	0	0
$BaSO_4$/Sorbitol	0	1	0	0–1*

* Variable.

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* Based on a paper given to a combined meeting of The British Institute of Radiology, Faculty of Radiologists, and the Royal Society of Medicine (Radiology Section) at the Royal College of Surgeons of England in January 1975.

rinsed in tap water to remove ingested material. The specimens were then filled with the barium sulphate suspension to be tested, drained, and then inflated with air. Radiographs were obtained in this air contrast phase.

TABLE II

The small intestine—scoring for mucosa

Barium preparation	*In vitro*		*In vivo*	
	Detail	Coating	Detail	Coating
Micropaque	3	2–3*	2	3
Baritop	2–3*	2–3*	1	2
Liquibarine	1–2*	1–2*	0	0–1*
High density preparation	2–3*	3	2	3

* Variable.

The radiographs were examined by four observers independently and a scoring system was used to assess the quality of fine mucosal detail and mucosal coating.

For fine detail (areae gastricae or jejunal mucosal pattern) the scores given were as follows: excellent—3; good—2; poor—1; and absent fine detail—0. Similarly, for coating of the mucosa, the scores given were: excellent—3; good—2; patchy—1; and very poor or no adherence—0.

The barium sulphate suspensions used for the studies were Micropaque (Nicholas Laboratories), Baritop (Concept Pharmaceuticals), Liquibarine (Norgine), an experimental high density preparation, and barium sulphate suspended in Sorbitol (Embring and Mattsson, 1968). For some parts of the investigation Gastrografin (Schering) was added to the barium sulphate in the proportions recommended by the manufacturers, *i.e.* two to three parts of barium to 30 ml of Gastrografin.

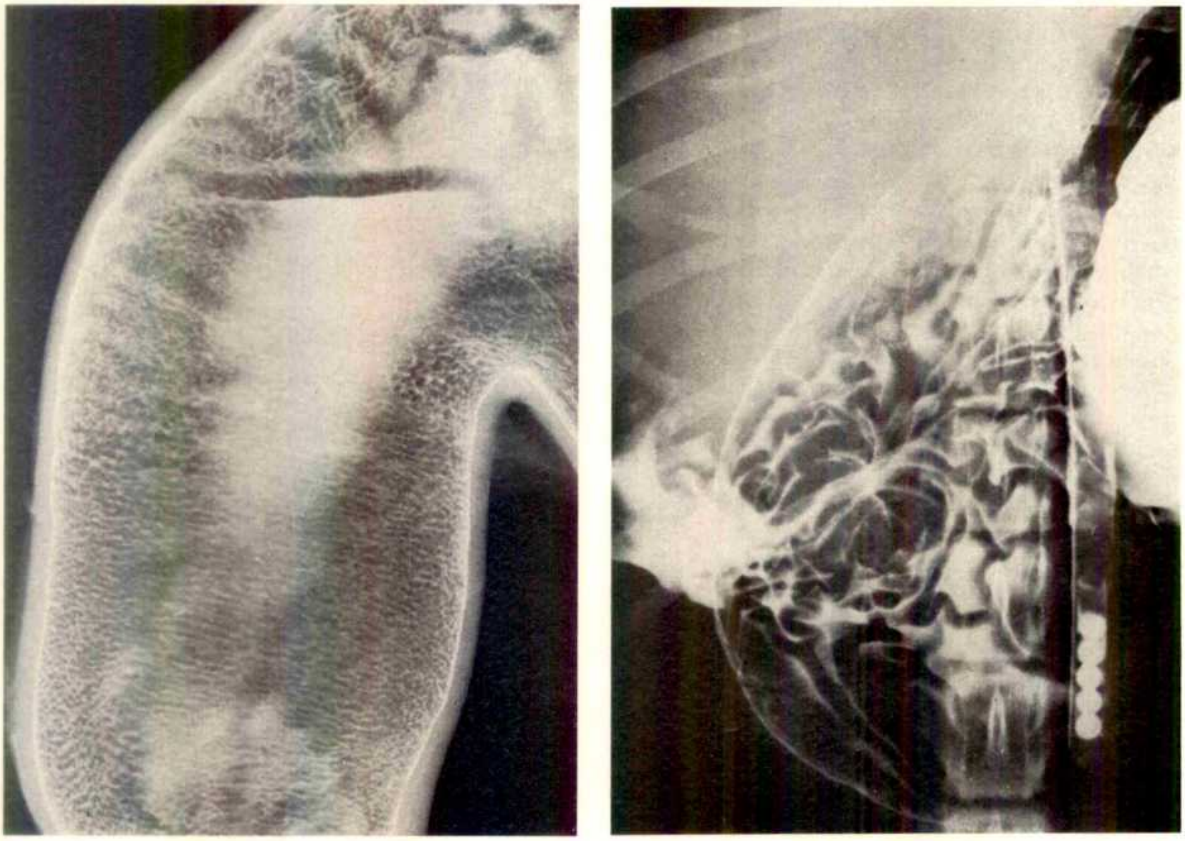

Fig. 1.
The stomach, using Micropaque: (A) *in vitro*; (B) *in vivo*.

Results

The results of the assessment of the radiographs are summarized in Tables I and II.

The stomach

Mucosal detail was poor in the *in vivo* studies—no areae gastricae were visible with any of the suspensions. Mucosal coating was variable *in vivo*, the best results under the conditions of these experiments being obtained with Micropaque, with Liquibarine being almost as good in this respect. This was in contrast to the result of the *in vitro* tests where good results were obtained though inconsistently with Baritop and the high density preparation. Double contrast studies with Micropaque gave the most consistent high scores for detail and coating (Fig. 1).

The most marked discrepancies occurred with the high density preparation and with Liquibarine. The high density preparation gave good results *in vitro*, but the results *in vivo* were poor (Fig. 2), whereas Liquibarine gave good results *in vivo* but poor results *in vitro*.

Further experiments were performed using the high density preparation and good mucosal coating was obtained *in vivo* after prior instillation of 10 ml of sodium bicarbonate solution into the stomach. The effect was, however, transient and the quality of coating reverted to its usual uneven, patchy appearance within five minutes.

The small intestine

Consistently good results were achieved with all the barium suspensions *in vitro* with the exception of Liquibarine. Fine mucosal detail was good although the evenness of coating varied from suspension to suspension. The best results *in vivo* were obtained with Micropaque and the high density preparation.

Further experiments were performed after diluting the barium suspensions with water to 50% of

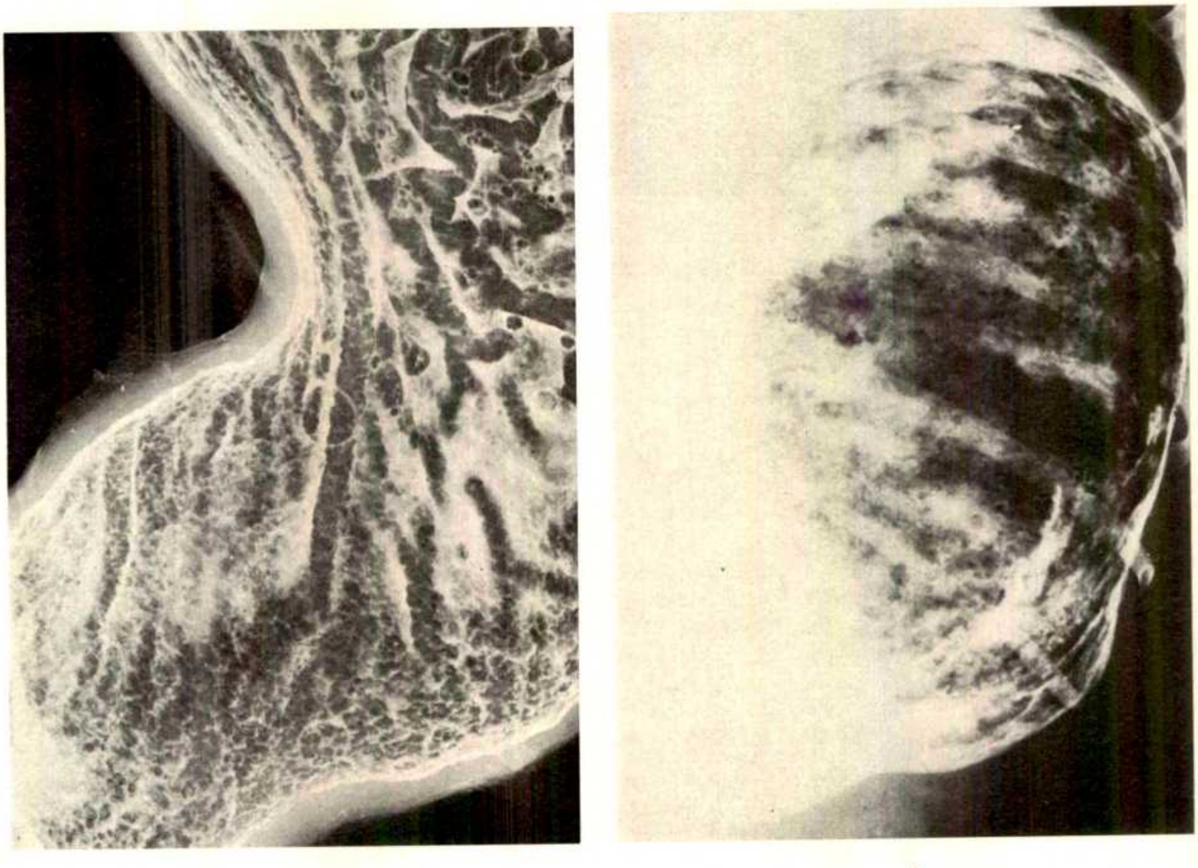
A B

Fig. 2.

The stomach, using a high density barium sulphate suspension: (A) *in vitro*; (B) *in vivo*. Note the poor coating in (B).

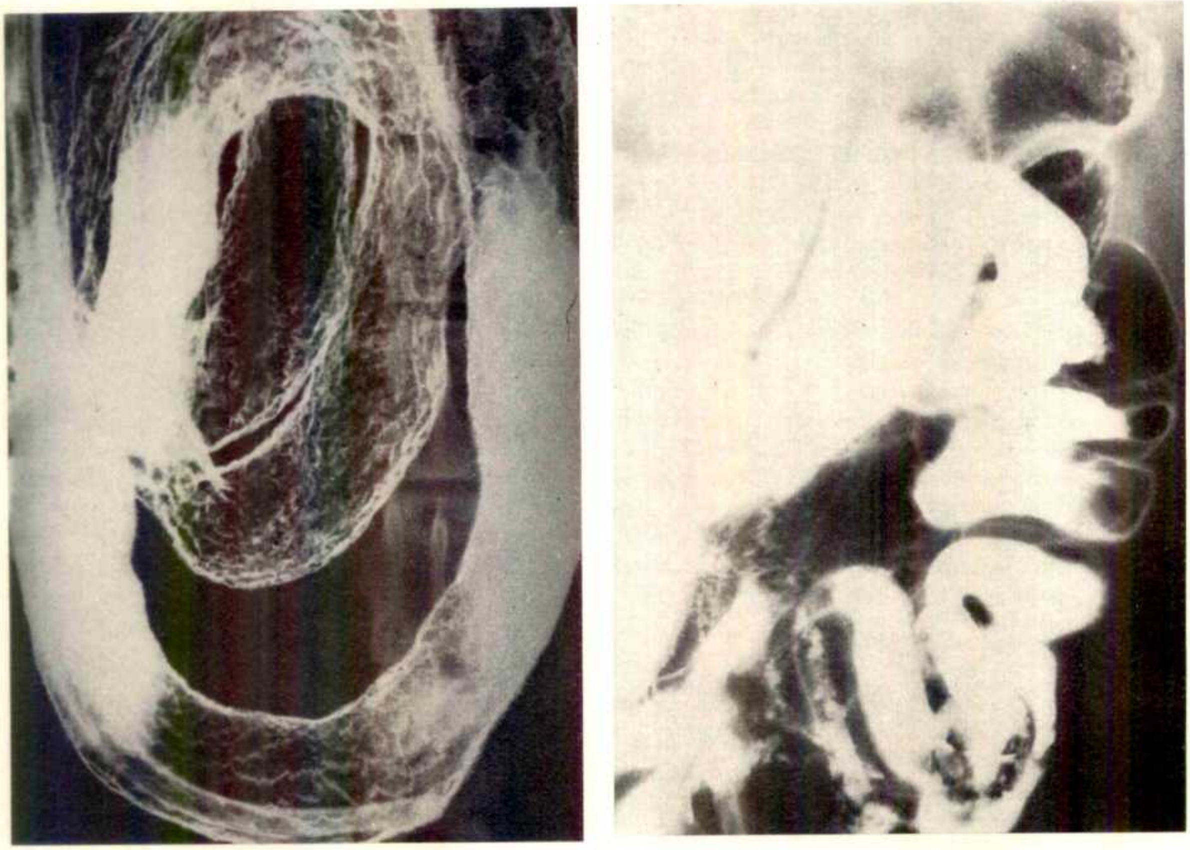

FIG. 3.

The small intestine *in vivo*, using Micropaque in (A), and Micropaque with Gastrografin in (B). The same animal was used for both studies.

their recommended concentration, and also after the addition of Gastrografin to the suspension. There was no change in the *in vitro* scores after either manipulation, but dilution with water adversely affected the results *in vivo* in all the suspensions except Micropaque, where the double contrast studies *in vivo* remained of a high quality. However, the addition of Gastrografin to the barium produced very poor small intestinal studies *in vivo* in all the barium suspensions tested including Micropaque (Fig. 3).

DISCUSSION

The gastric mucosa in the dog has two distinct patterns—the plicae gastricae or rugal folds, and the areae gastricae. The latter consist of small raised areas which are elongated in shape in the pyloric region but polygonal elsewhere in the stomach (Miller *et al.*, 1964). The delineation of these minute units of gastric mucosal anatomy has been considered to be a measure of the success of double contrast radiology of the stomach in human beings (Kreel *et al.*, 1973).

The small intestinal mucosa in the dog has a smooth velvety surface consisting of innumerable intestinal villi (Miller *et al.*, 1964). The radiological appearance of the mucosa of the small intestine in dogs is less complex than in human beings (Fig. 3) as there are no valvulae conniventes in the small intestine of the dog.

It was decided to study the small intestine in the same way as the stomach in this investigation because preliminary work with a high density barium sulphate suspension had shown a marked discrepancy between its behaviour in the canine stomach and small intestine.

On the basis of his *in vitro* experiments, Kreel *et al.* (1974) found undoubted superiority of one barium suspension over others in delineating mucosal detail, without undesirable features such as bubbling, dense flecks, or thick coating to obscure the detail obtained.

The results of the present study indicate that there are discrepancies between the coating properties of most barium sulphate suspensions in the stomach, depending on whether they are tested *in vitro* or *in vivo*. Similarly, most of the barium suspensions gave inconsistent results in the small intestine. Under the conditions of our experiments only Micropaque gave consistently good double contrast radiographs *in vivo* and *in vitro* in both organs.

It is concluded that *in vitro* testing of barium sulphate suspensions is of limited value in assessing the efficiency of the suspensions in coating the mucosa of the stomach or small intestine in the dog. As there are physiological differences between human and dog stomachs, clearly any suspension has to be tested in the provocative environment in which it eventually has to be used as a diagnostic tool before its relative merits and disadvantages can be critically evaluated.

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Double contrast preparations: an *in vitro* study of some antifoaming agents

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Abstract

An apparatus is described for the study of foam formation in double contrast preparations *in vitro*. Antifoaming agents are shown to be of considerable benefit to the double contrast technique, silicone and silicone-free antifoamers being equally effective. Silicone antifoamers are preferred because of their wide clinical acceptability. Antifoamer formulation and concentration are found to be critical factors in determining efficacy of foam suppression, and may lead to erroneous results in the clinic.

The double contrast barium meal is well established (Kalokerinos, 1967; Buonocore and Meaney, 1966; O'Reilly and Bryan, 1974; Kreel *et al.*, 1973) and several methods have been published for the introduction of gastric gas. Intubation is the most direct, particularly if combined with a barium spray to facilitate mucosal coating (Buonocore and Meaney, 1966) but has low patient tolerance (O'Reilly and Bryan, 1974). A more simple technique is to generate the required gas *in situ* by effervescent tablets or a two-part bicarbonate/citric acid barium preparation (O'Reilly and Bryan, 1974). Alternatively, the barium preparation can be precarbonated in a domestic soda syphon (Pochaczevsky, 1973), purchased as a commercial precarbonated product (Baritop-100—Concept Pharmaceuticals), or prepared *in situ* by consecutive swallowing of barium sulphate suspension and soda water (Delestre and Godlewski, 1975).

However, foam formation may lead to poor mucosal definition and mucosal coating, while trapped air pockets make radiological interpretation difficult. Some procedures therefore employ a polydimethylsiloxane antifoaming agent in the barium preparation (O'Reilly and Bryan, 1974; Kreel *et al.*, 1973; Obata, 1972), in the effervescent tablet (Baritop tablets—Concept Pharmaceuticals), or separately (Kalokerinos, 1967). As a further precaution, the viscosity of the barium preparation may be lowered by the addition of sodium citrate (O'Reilly and Bryan, 1974).

However, there is only one published report (O'Reilly and Bryan, 1974) and one commercial claim (Baritop tablets—Concept Pharmaceuticals), that polydimethylsiloxanes have any value as antifoamers for barium sulphate suspensions, and we have been unable to find any references to alternative antifoamers. In view of the increasing use of the double contrast technique we have therefore studied the efficacy of a number of conventional antifoaming agents against barium sulphate foams and the results of our studies are presented in this paper. All experiments are based on a clinical procedure in which a patient washes down four crushed potassium tablets or 40 crushed Baritop tablets with 100 cm^3 undiluted Baritop-100 or 50:50 Micropaque/water containing a known concentration of antifoaming agent. As an indication of the effect of excessive dilution, 25:75 Micropaque/water has also been considered. While it is recognized that alternative clinical procedures may lead to less foaming per se, these conditions are particularly suitable for the study of antifoaming additives because they optimize the formation of foam.

For convenience, all experiments are quarter scale.

Foam Formation and Collapse

Foam collapse occurs via gravity drainage until bubble walls are sufficiently thin to rupture by Brownian motion. Foam stability of any liquid can then be estimated either from the equilibrium foam height caused by a constant gas stream through the liquid, or by shaking a standard liquid volume with a standard gas volume and measuring the subsequent foam collapse.

The chosen clinical situation is a compromise between these because although gas production is rapid and approximates to foaming by shaking, it is not instantaneous and some foam collapse occurs before formation is complete. A simple calibrated apparatus has therefore been designed to model this clinical situation rather than any standard foam test, as described below.

Experimental

Materials

Micropaque was obtained from Nicholas Laboratories Ltd., effervescent potassium tablets from Thomas Kerfoot and Sons, and Baritop tablets and Baritop-100 from Concept Pharmaceuticals.

Representative polydimethylsiloxane antifoamers were obtained from Nicholas Laboratories Ltd.

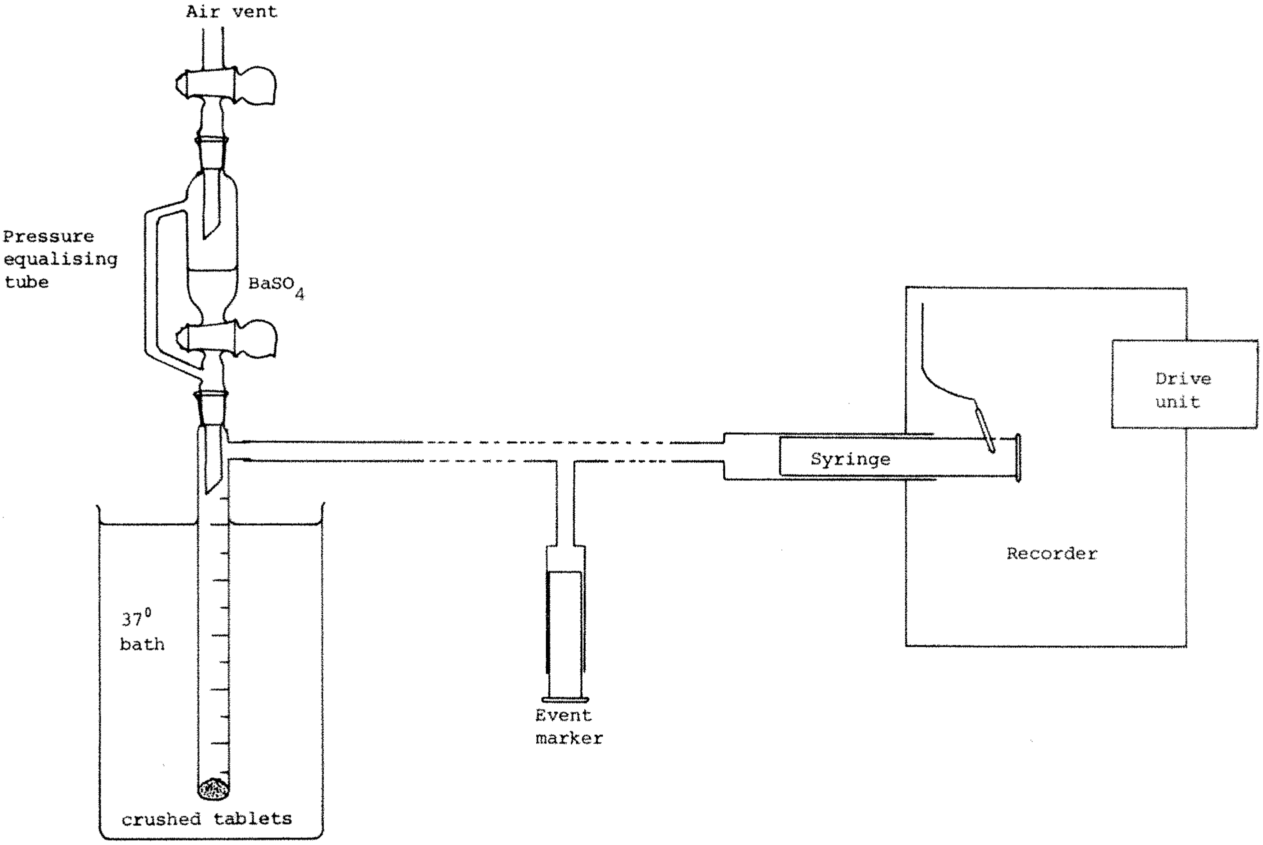

FIG. 1.
Apparatus for studying foam formation and inhibition in double contrast preparations.

(Polycrol Forte Gel), Berk Pharmaceuticals Ltd. (Asilone suspension), Carter Wallace Ltd. (Sovol), Hopkin and Williams Ltd. (Hopkin and Williams antifoamers), Imperial Chemical Industries (ICI Silcolapse 437), and Basildon Chemical Co. Ltd. (Basildon antifoamers).

Representative silicone-free antifoamers were obtained from Compounding Ingredients Ltd. (Cilfoam T5934), Diamond Shamrock Chemicals (UK) Ltd. (Nopco Foamasters), and Sipon Products Ltd. (Sipon antifoamers).

Apparatus

A volume-calibrated tube 37 cm × 3 cm and sealed at one end was surmounted by a dropping funnel fitted with a pressure equalizing arm, and placed in a water bath at 37±0.1°C. A side arm led to an Exelo gas syringe recorder (Messrs. Griffin and George Ltd., England) as shown in Fig. 1. The recorder response was essentially linear up to 100 cm^3 with an error of ± 1%.

Method

A 10% $^w/v$ dispersion of antifoaming agent in 50:50 Micropaque/water was serially diluted to give antifoamer concentrations of 1%, 0.1% and 0.01% $^w/v$. For each of the four concentrations 25 cm^3 was then run rapidly on to one crushed effervescent potassium tablet at 37 deg in the calibrated tube of Fig. 1. Gas volume, gas production profile, maximum foam volume (assuming 25 cm^3 liquid below) and foam collapse time from maximum height were then recorded. The experiments were then repeated with 25:75 Micropaque/water.

Baritop tablets were used only in preliminary studies which indicated no advantage over potassium tablets with either Baritop-100 or Micropaque, in spite of their content of polydimethylsiloxane. Baritop-100, although gaining in popularity as a double contrast agent, was also used only for preliminary experiments because of problems associated with its presentation as a precarbonated can, *viz.* (i) the evolution of its own gas was considerably slower than that due to the effervescent tablets, and was associated with a slow secondary foam formation, and (ii) the volume of gas evolved from any one can was found to depend critically upon the ambient temperature, the time from opening the can to beginning any one experiment, and the extent of shaking required to resuspend any settled barium sulphate before the can was opened. Fifty per cent Micropaque was used in preference to 100% Micropaque to approximate to the viscosity of Baritop, thus avoiding the complication of bubble entrapment in viscous systems.

Results

Gas production

One effervescent potassium tablet was found to weigh 1.23±0.02 g and produce 85±5 cm^3 carbon dioxide. In preliminary experiments ten Baritip tablets were found to weigh 0.86±0.03 g and produce 85±5 cm^3 carbon dioxide. Preliminary experiments also indicated that the solubility of carbon dioxide in 50:50 Micropaque/water was negligible.

Foam formation and collapse

Typical results for the most effective silicone-containing and silicone-free antifoaming agents are shown in Tables I–IV, the time to produce 90% of the total gas evolved being arbitrarily taken as an indication of the rate of gas evolution.

Discussion

The availability of a simple antifoaming agent for use with currently available barium preparations in double contrast procedures would considerably enhance the development of this new technique. However, the efficacy of antifoaming agents is greatly dependent upon the nature of the system being studied, so that in the case of gastric contents such factors as pH, mucin content, food remnants and saliva should ideally be considered in addition to the barium sulphate suspension. This leads to certain problems of experimental design in that it becomes difficult to define the "ideal" stomach contents, and in any event a patient with gastric problems is unlikely to present standard gastric conditions. The work described in this paper has therefore been limited to studying the foaming properties of the barium preparation per se, and we cannot say whether the presence of other gastric constituents would alter our results.

Gas production rate

It is not unreasonable to expect that the addition of foam suppressants might affect gas production by interfering in some manner with the process of effervescence. If this interference were non-specific (*e.g.* simply an alteration in the viscosity of the system) it might also be expected that the gas production rate should correlate with antifoam concentration.

TABLE I

Most effective silicone antifoamers for 50:50 micropaque/water

Antifoamer	Conc^n., %	Foam volume, cm^3	90% gas time, sec	Foam collapse time, sec
Basildon Antifoamer FD	1	17	31	14
ICI Silcolapse 437	0.1	26	30	20
Hopkin and Williams Antifoam Emulsion RD	1	17	41	14
Control	0	31	54	90

TABLE II

Most effective silicone antifoamers for 25:75 micropaque/water

Antifoamer	Conc^n., %	Foam volume, cm^3	90% gas time, sec	Foam collapse time, sec
Hopkin and Williams DC Antifoam Emulsion M-30	1	12	12	7
Hopkin and Williams DC Antifoam M	0.1	28	14	13
ICI Silcolapse 437	1	28	24	6
Control	0	37	8	53

TABLE III

MOST EFFECTIVE SILICONE-FREE ANTIFOAMERS FOR 50:50 MICROPAQUE/WATER

Antifoamer	Conc^{n}., % ^{w}/v	Foam volume, cm^{5}	90% gas time, sec	Foam collapse time, sec
Sipon Antifoamer VP–BE 7205	1	8	30	10
Nopco Foamaster NXZ	1	11	27	17
Nopco Foamaster JMY	1	14	27	19
Control	0	31	54	90

TABLE IV

MOST EFFECTIVE SILICONE-FREE ANTIFOAMERS FOR 25:75 MICROPAQUE/WATER

Antifoamer	Conc^{n}., % ^{w}/v	Foam volume, cm^{3}	90% gas time, sec	Foam collapse time, sec
Nopco Foamaster JMY	1	11	17	11
Sipon Antifoamer VP–BE 7184	10	3	30	0
Cilfoam T5943	1	8	18	13
Control	0	37	8	53

In Tables I and III, it can be seen that the most effective antifoaming agents cause a considerable reduction in 90% gas times for 50:50 Micropaque/water. This effect was found to be linked to the efficacy of the antifoamer, and was not significant for some of the poorest candidates studied. More importantly, no antifoamers showed the concentration/gas rate correlation expected of a non-specific interaction, most compounds passing through an optimum concentration of 1% or 0.1% ^{w}/v.

Dilution to 25:75 Micropaque/water always accelerated gas production compared with the equivalent experiment at the higher concentration. In all cases, however, the addition of the antifoamer retarded gas production compared with the control experiment, as can be seen from Tables III and IV.

Maximum foam volume

Foam volume as measured in this paper is related to many factors, including rate of foam formation, rate of foam collapse, effervescent particle size and liquid viscosity, so that an absolute interpretation of the measured foam volume is difficult. However, for 50:50 Micropaque/water (Tables I and III) the 90% gas times are of the same order, so that to a first approximation maximum foam volumes are directly comparable. For all antifoaming agents, the concentration which gave the most rapid gas evolution also gave the lowest maximum foam volume.

Foam collapse times

Foam collapse time is perhaps the most important guide to foam stability. For all antifoaming agents studied, the most effective concentration was that which also produced maximum gas production rate and minimum foam volume. It would thus seem that these three parameters are highly correlated and may have a common origin.

More importantly, all antifoaming agents exhibited, in addition to concentrations at which the foam was destabilized, at least one concentration which enhanced foam stability. An interesting case is that of the clinically acceptable silicone preparation Polycrol Fotre Gel which conferred a pronounced stability on barium sulphate foam at 10% and 1% ^{w}/v, in spite of the success of most other silicone preparations at these concentrations. The effect may be due to other additives (such as flavouring agents). It would thus appear that unless care is taken in the use of antifoamers in the clinic, the addition of a proven antifoamer in the wrong proportions might actually promote the very result which it is desired to eliminate.

Comparison of silicone and silicone-free antifoamers

Polydimethylsiloxanes have received wide use as clinically acceptable antifoaming agents. On the other hand, there have been no reports of silicone-free antifoaming agents for double contrast procedures, other than the use of sodium citrate to lower viscosity of the barium preparation (O'Reilly and Bryan, 1974). Since effervescence is achieved through the reaction of sodium bicarbonate and citric acid, the addition of extra sodium citrate might seem unnecessary. In all experiments carried out by us, we have observed that effervesced Micropaque settles more rapidly than untreated Micropaque, suggesting that the viscosity could indeed have been lowered. However, there are many other commercially available silicone-free antifoamers which have not been passed for use in pharmaceutical preparations. Among those which might be mentioned are alcohols, fatty acids and their esters, amides and phosphates (L. I. Osipow, *Surface Chemistry*, pp. 373–374, Rheinhold). In particular, silicone-free antifoamers are employed in foam suppression when carbonate rock is treated with acid (*e.g.* Armoflo 49—Armour Hess Chemicals Ltd.), a situation not unlike that presented by effervescent tablets.

It is evident from Tables I and III that neither series of antifoamers offers any clear advantage over the other except perhaps in terms of foam volume, which is in any event not as clinically significant as gas rate and foam collapse time (see below). In at least one case it was possible to obtain the same silicone-free preparation with and without added silicone (Sipon antifoamers VP–BE 7184 and VP–BE 7205 resp.) and demonstrate this directly. Since polydimethylsiloxanes have already been passed for pharmaceutical use, there would appear to be no advantage in seeking alternative agents.

Clinical significance

From the clinical viewpoint, the most important parameter is perhaps the total time from administration to complete foam collapse, irrespective of the absolute amount of foam produced. If the 90% gas time is taken as an approximation to the full effervescence time, then the sum of 90% gas times and foam collapse times is a reasonable guide to what might be expected in the clinic. From Tables I and III for 50:50 Micropaque/water, it can be seen that the effect of adding antifoamer is to reduce the control time (144 sec) by a factor of 2.6–3.6. Silicone antifoamers would therefore appear to be of significant advantage to the double contrast technique, particularly since they are also known to suppress mucus foam (Rider and Moeller, 1960; Oswald, 1961), and are clinically acceptable.

Three further points must, however, be considered. As mentioned previously, Polycrol Forte Gel enhances foam stability, suggesting that not all silicone preparations are equally effective. Also as mentioned previously, it would appear that the optimum antifoam concentration is 1% or 0.1% /^{w}v, and that addition of the wrong proportion of antifoamer could actually stabilize gastric foam. Thus the reported use of Simethicone at 100 ppm (0.01%) could be on the low side (Obata, 1972), and we would recommend that potential silicone antifoamers be tested at these two concentrations preferentially. Thirdly, in our experiments the polydimethylsiloxane in Baritop tablets has little or no effect in suppressing-foam formation compared with effervescent potassium tablets, and we consider that it would be necessary to add a supplementary antifoamer with the former.

Finally, if our results are applicable to the clinical situation, we consider the search for silicone-free antifoamers to be unnecessary, and the addition of selected silicone antifoamers to be one possible solution to the problem of double contrast foam formation.

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The concentration maximum concept in intravenous cholangiography

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ABSTRACT

The excretion of ioglycamate in the bile of the rhesus monkey was measured at 5% and at 100% bile diversion following an intravenous bolus injection of ioglycamate. At 100% diversion the bile volume was reduced and the concentration of ioglycamate was increased, but the quantity excreted was unchanged. A similar study using iodipamide reported previously gave the same result. When the ioglycamate was given by intravenous infusion, the effect of 100% bile diversion was quite different. The concentration of ioglycamate in the bile was unchanged by the bile diversion but the excretion was reduced. These results indicate that the transport maximum for the excretion of ioglycamate in bile is not a constant and is reduced by interruption of the enterohepatic circulation of bile salts. The maximum concentration of ioglycamate in bile was constant and was independent of the reduction in bile salt output produced by 100% bile diversion. Following a single bolus injection however, the reduction in bile flow produced by 100% bile diversion increased the biliary concentration of ioglycamate. These results suggest that the excretion of ioglycamate is limited by a maximum concentration rather than a transport maximum. The maximum rate of transport (Tm) is dependent on two factors—the maximum concentration of ioglycamate in the bile and the rate of bile flow. The maximum concentration is achieved by an infusion technique and not by a single bolus injection and this supports the view that an infusion technique should be used for intravenous cholangiography.

The importance of maintaining an intact enterohepatic circulation of bile salts when measuring the excretion of biliary contrast media has been reported previously (Whitney and Campbell, 1972). Interruption of the enterohepatic circulation by 100% diversion reduced the bile volume and increased the concentration of iodipamide in the bile following a bolus injection—the same quantity was excreted in a smaller bile volume. When we looked at the effect of 100% bile diversion on the excretion of ioglycamate, the result was quite different. The concentration of contrast medium in the bile was unchanged, but the transport maximum (Tm) was reduced. For the ioglycamate experiments, an infusion technique had been used, whereas a bolus injection was given in the iodipamide study. The conflicting results could have been due to differences between iodipamide and ioglycamate or to differences between a bolus injection and an infusion. The ioglycamate experiments were repeated using a bolus injection instead of an infusion. The present paper reports the results of measuring the excretion of ioglycamate in the bile of the rhesus monkey at 5% and at 100% bile diversion following an infusion and following a bolus injection of ioglycamate.

MATERIALS AND METHODS

Experimental animals

The experimental model has been fully described elsewhere (Dowling *et al.*, 1968). Female rhesus monkeys weighing approximately 4 kg were used. The animals had a T-tube tied in the common bile duct in such a manner that the cannula collected both hepatic and gall-bladder bile. The common bile duct was occluded so that all the bile was collected by the cannula. The bile was passed through an electronic stream splitter to divert one drop in 20 for analysis. The remaining bile was returned via a second T-tube inserted into the gastric antrum. Both cannulae were exteriorized through separate stab wounds. The monkeys were kept in restraining chairs and were not used in experiments until the bile volume and bile salt secretion reached a steady state; this usually took at least two weeks from the time of operation.

Experimental technique

Using the injection technique, 850 mg of meglumine ioglycamate labelled with a tracer dose of ^{125}I in 5 ml of normal saline was injected intravenously over four minutes. Using the slow infusion the same compound was given intravenously by an electrical pump at 26 mg/min for 120 minutes. The experiments were in two parts. In the first part, one drop of bile in 20 was removed by the stream splitter for analysis and the remaining 19 drops were returned to the intestine (5% diversion). In the second part, conducted within a week of the first, no bile was returned to the intestine (100% diversion). The appropriate state of diversion was maintained for three days before each experiment. The results were used in the series only if the bile volume and composition were steady for at least two days before and two days after the experiment. During the experiment the T-tube in the common bile duct was disconnected from the stream splitter and serial ten-minute collections of bile were made. The volume of each sample was noted and 0.2 ml was taken for estimation of ioglycamate. The rest of the collection was returned to the intestine or discarded if there was 100% diversion. The amount of bile removed would not be expected to affect the enterohepatic circulation (Dowling *et al.*, 1970). The concentration of ioglycamate in each sample was estimated by comparing its radioactivity with that of a stock solution, using a well type scintillation counter. The rate of excretion was calculated by multiplying the concentration by the bile volume.

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Calculations

Six pairs of experiments were carried out on three animals using the injection technique. Five pairs of experiments were carried out on three animals using the infusion technique. "Peak concentration" of ioglycamate is the concentration averaged over the 30-minute period during which the concentration was maximal. The "transport maximum" is the average rate of excretion during the 30-minute period that output of ioglycamate in the bile is maximal. This measurement applies when a continuous infusion of ioglycamate is given intravenously which is sufficient to achieve the maximum rate of hepatic excretion. Paired T-tests were used to analyse the results.

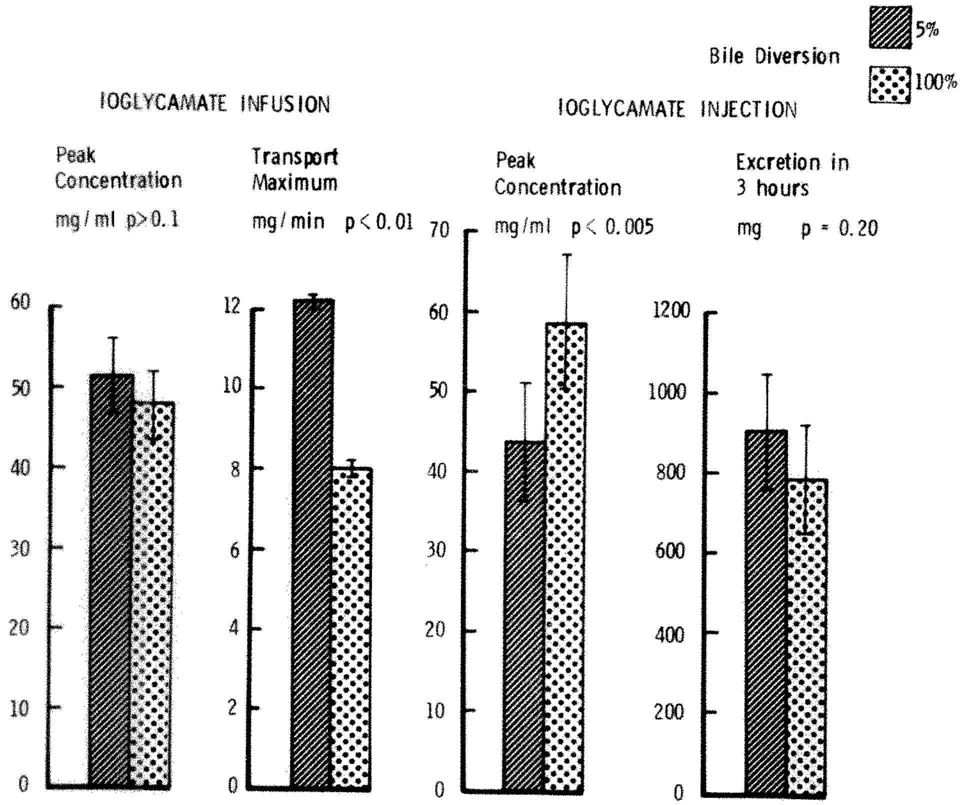

FIG. 1.

Ioglycamate concentration and excretion in the bile following intravenous injection or infusion at 5% and at 100% bile diversion. The monkeys with 100% bile diversion had a higher peak concentration than those with 5% diversion with a single bolus injection, but there was no difference with an infusion. The excretion rate was greater for the monkeys with 5% diversion of bile when the infusion was used, but was not different with the bolus injection.

Results

The results at 5% and at 100% diversion are compared in the histogram (Fig. 1). Using the infusion technique, there was no significant difference in the peak concentration of ioglycamate. The transport maximum was 12.1 mg/min at 5% bile diversion and was 8.05 mg/min at 100% diversion, a significant decrease ($p < 0.01$). Using the injection technique, the total excretion of ioglycamate in three hours was not significantly different for either group. The peak concentration at 5% bile diversion was 43.7 mg/ml and at 100% diversion 58.7 mg/ml, an increase of 34%, which was significant ($p < 0.005$).

Discussion

Initially, the effect of 100% bile diversion on the excretion of ioglycamate when given by an infusion was studied. The bile volume and the excretion of ioglycamate in the bile was reduced, but the concentration of ioglycamate was unchanged. This result differed unexpectedly from that reported previously for iodipamide (Whitney and Campbell, 1972). In that study the reduction in bile volume which was produced by 100% bile diversion was accompanied by a proportional increase in the biliary concentration of iodipamide so that the output of iodipamide was unchanged. This discrepancy could be explained either by differences between iodipamide and ioglycamate or by the method of administration. The iodipamide was given by a bolus injection, but an infusion of ioglycamate was used. The experiments were repeated using the bolus injection technique with ioglycamate. The same result was obtained as was found previously with iodipamide. This suggested that the difference was due to the method of administration. With the bolus injection method, the change from 5% to 100% bile diversion increased the concentration of ioglycamate in the bile, whereas the concentration did not increase when the infusion method was used.

The results indicate that there is an upper limit for the concentration of ioglycamate in canalicular bile, a concentration maximum. A similar system has been described for bromosulphthalein (O'Maille *et al.*, 1966). In that study the transport maximum was considerably increased by a simultaneous infusion of cholate, but the biliary concentration was unchanged. In the present experiments, a similar effect on ioglycamate excretion was observed when the bile salt output and bile volume were increased by the change from 100% to 5% bile diversion. The same result has been demonstrated in dogs, using infusions of iodipamide (Benness and Raine, 1971). The increase in the excretion of contrast medium associated with greater bile flow produced by the increase in bile salt excretion is unlikely to improve the radiographic image, since it is the concentration of iodine in the bile, not the total amount of iodine which determines the radiographic density (Edholm and Jacobson, 1959).

Canalicular bile is modified in the hepatic ductules either by secretion of bicarbonate-rich fluid or by reabsorption of water (Sperber and Sperber, 1971). The choleresis produced by secretion is due to increased ductular fluid output and since this is distal to the site of excretion of bromosulphthalein (BSP), it does not increase the transport maximum of BSP, unlike the choleresis produced by an infusion of bile salts (O'Maille *et al.*, 1966). Increased bile flow at the ductular level merely dilutes the bile. Conversely, a reduction in ductular fluid production by atropine or pipenzolate methylbromide increases the biliary concentration of iodipamide in dogs (Burgener *et al.*, 1976).

Biliary contrast media cause a large choleresis, due to the secretion of osmotically active molecules into the bile. The bile tends to remain isosmotic with plasma (Sperber and Sperber, 1971). Elevation of the plasma osmolality by hypertonic dextrose transiently increases the biliary concentration of iodipamide (Benness and Soschko, 1972).

When ioglycamate was given by a bolus injection, the concentration of ioglycamate in the bile was increased by changing from 5% to 100% diversion, but the quantity excreted was unchanged. The reduction in bile flow produced by 100% bile diversion should not be able to increase the concentration of ioglycamate in the bile since we have already established that there is a concentration maximum for ioglycamate. The increase in the concentration of ioglycamate in the bile observed following 100% bile diversion in monkeys receiving a bolus injection of ioglycamate means that the excretion following the bolus injection is less than the maximum concentration. The maximum concentration is, however, achieved by the infusion technique. This would explain the observation that the concentration of iodipamide in the bile is higher following an infusion than following a bolus injection (Whitney and Bell, 1972) and supports those authors who have found that an infusion technique yields better cholangiograms than does a single bolus injection (McNulty, 1968; Allen, 1969).

The concentration maximum concept also means that provided that an infusion technique is used to reach the concentration maximum it will only be possible to improve cholangiograms by one of two methods. Either techniques will have to be developed to remove water from the bile distal to the hepatocyte, that is, from ductular bile, or the iodine content of the contrast agent will have to be increased so that its osmotic activity per atom of iodine is reduced. Improvements in the excretion of the contrast agent can only cause a corresponding increase in bile volume once the concentration maximum has been reached.

Acknowledgments

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An evaluation of transverse axial emission tomography of the brain in the clinical situation

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ABSTRACT

The Aberdeen section scanner provides, in addition to conventional views, a display of the distribution of radioactivity in a tomographic section of the brain. This paper examines the value of this additional information. Scans of lesions confirmed pathologically or radiologically, along with normal and doubtful cases, were examined after a careful randomization procedure. During the course of the study each set of conventional views was examined twice, once without and once with a tomographic section view. In two out of 29 cases (7%) the lesion was diagnosed only with the aid of the tomographic section scan. Improved accuracy of diagnosis with the tomographic section view was significant at the 1% level or better.

Routine services for the provision of γ-ray emission pictures of the brain following injection of radioisotope, either by gamma camera or rectilinear scanning, are now available in a large number of centres. Isotope brain scanning is a well-established procedure and the diagnostic importance of this examination requires no justification. In general, reports are made on four conventional views, anterior, posterior and right and left lateral. Since 1968 the Department of Medical Physics in Aberdeen has developed and progressively improved the technique to obtain transverse section views of the brain at one or more levels in addition to the conventional view (Bowley *et al.*, 1973; Keyes, 1976). The purpose of the present paper is to assess the value of the additional information provided.

One way to evaluate the tomographic view would be to design a model system, *e.g.* a set of phantoms containing bottles which could be examined by conventional or conventional plus tomographic methods. However, it was not considered possible to design a sufficiently complex model test system to simulate the use of tomography in the clinical situation. We have therefore used data taken with patients to test the value of the tomographic view.

It must be emphasized that this paper will not attempt to assess the overall diagnostic accuracy of radioisotope brain scanning either with or without tomography. For the purpose of the exercise it was necessary to withhold clinical information that would normally be considered during reporting (for example the clinical summary of the patient's condition). Clearly such information makes an important contribution to the overall conclusion, and diagnostic predictions cannot be as accurate when it is withheld.

The investigation was therefore designed primarily to answer one simple question. Is the information that can be deduced from images of radioisotope distribution in the brain more accurate and useful with conventional views plus one or more tomographic views, than with conventional views alone?

A cursory examination of this problem might suggest that the tomographic view must be useful because it is additional to the conventional view. However, quite apart from the fact that this advantage might be minimal, the premise itself is not necessarily valid. Certainly the tomographic view will provide extra data, but if the information contained in the tomographic view were unreliable, a possibility that will be considered briefly in the discussion, the overall deductions might be less reliable in the clinical situation. The electrical analogy is the degradation of transmitted signals by noise.

METHOD

The parameters considered most suitable for describing a set of brain scans are specified in detail in Table I. They may be used whether a tomographic view is available or not.

The salient features are:

1. Evidence of abnormality is marked out of a maximum of five. Thus a set of scans considered within normal limits is given an abnormality rating of zero.
2. The position, shape and depth of the lesion is recorded, but if two or more sub-categories cannot be differentiated, ten points are distributed between them.
3. The size of the lesion is estimated in centimetres.
4. A qualitative estimate of intensity of any abnormal uptake is used to include both increased radioactivity and area of abnormal uptake. The increase in colour bands above the normal colour

TABLE I

Details of the parameters recorded for each set of scans

1. *Abnormality rating*—scored out of a maximum of five.

2a. *Position of lesion*
    - frontal
    - parietal
    - temporal
    - occipital
    - posterior fossa
    - petrous
    - multiple

2b. *Depth of lesion*
    - left
    - right
    - deep
    - parasagittal
    - superficial

2c. *Shape of lesion*
    - spherical
    - diffuse
    - flare shape
    - lobulated
    - multiple
    - surface

3. *Size of lesion* (cm)

4. *Intensity of uptake?*
    - (a) Qualitative estimate (maximum five)
    - (b) How many colours above normal?

5. *Diagnosis*
    Assuming the scans are abnormal, what is the best estimate, on the available data, of the diagnosis? primary tumour or single secondary; multiple secondaries; subdural; cerebral haemorrhage; meningioma; infarct/contusion; pituitary tumour; abscess; vascular anomaly; acoustic neuroma.

TABLE II

Independently confirmed diagnosis for the 29 cases in the "abnormal group"

Primary tumour or single secondary	13
Acoustic neuroma	1
Pituitary tumour	1
Meningioma	4
Multiple secondaries	3
Infarct/contusion	2
Subdural/cerebral haemorrhage	5
Abscess	0
Vascular anomaly	0

level expected in that part of the scan is also estimated. This is a more objective parameter.

5. Finally, for all examinations awarded an abnormality rating of one or higher, a diagnosis is attempted on the scans alone. When only a differential diagnosis is possible, a total of ten points must be shared appropriately.

Scan data for this survey were selected from our files as follows:

(a) *The abnormal group*

Positive brain scans from patients where the pathological diagnosis had been definitely established by conventional neuroradiology, operation, biopsy, or post mortem, were selected from the records of 1974 to early 1976 by an independent neuroradiologist. These 29 cases constituted the "abnormal group" and their pathologies were distributed as shown in Table II. This information was not known to the examining team at the time of the survey.

(b) *The normal group*

Fifteen scans from early 1975 which had been reported normal by both physicist and radiologist and confirmed by at least one year of follow up were also selected. This constitutes the "normal group".

(c) *The equivocal group*

Since, in practice, a considerable proportion of scans are doubtful in varying degree, a third group of equivocal cases was selected to introduce a proper degree of complexity to the reporting process. These 13 cases were distributed randomly through the series, but no deductions have been made from the results of this group.

Fifty-seven sets of scans, printed out in colour using the statistical scale described by Smith *et al.* (1974) and evaluated by Sharp and Mallard (1976), were thus assembled. Each examination could be identified by its original scan reference number which was hidden from the reporting team.

In a retrospective study, the great danger is the introduction, either wittingly or unwittingly, of bias. This was eliminated as far as possible. First the 57 scan reference numbers were mixed by a standard randomization procedure. This produced series A, which was prepared for scrutiny without the tomographic view, and only the directing staff who arranged the scans could relate this sequence to the scan reference numbers.

The same 57 scan reference numbers were then randomized a second time to provide series B for examination with the tomographic view.

The team examining the scans comprised two physicists and two radiologists, together with a research fellow in nuclear medicine, all of whom had experience with this type of display. Since it was rarely possible to assemble all members of the team, one physicist and one radiologist constituted a quorum. For each set of scans, all the parameters listed in Table I were recorded.

Examination of scans from series A and B was made alternately. This meant that any change in scan appreciation applied equally to both series, that some cases were reported first with the tomogram and others without, and that both sets of scans for one patient might be examined in quick succession, or might be well separated.

Another potential source of bias was that the physicist or radiologist might remember the patient's original examination. To avoid this, the original reference number, name, date of examination and other data were covered up. The clinical summary was also withheld. The only information provided for the examining team was: (a) the position for the conventional views; (b) the section level of the tomogram, whether or not the tomogram was actually being shown.

When all the scans had been examined, 16 sets, eight with tomograms and eight without, were selected at random for re-examination. These comprised six from the "abnormal group", five from the "normal group" and five from the "equivocal group". These scans provided information on the consistency of the reporting method. No scan was re-examined for any other reason and, in particular, no scan was re-examined after collation of the results had begun. Except for analysis of consistency of reporting, all comparisons are based on the first report.

RESULTS

Before comparing reports for the same patient with and without the tomographic view, it was important to check that the system of reporting we had set up would give consistent results.

This could be done by analysing the results for the last 16 sets of scans, eight with tomograms and eight without, that were re-examined under identical conditions. Two parameters were considered particularly useful for this comparison. The first was the abnormality rating (item 1 in Table I), and the second the increase in the number of colours in the abnormal area (item 4b in Table I). These results are summarized in Table III. They show that the degree of abnormality is very difficult to assess consistently. An inconsistency of one or two in abnormality rating occurs quite frequently. An estimate of the increase in colour bands in the abnormal region is simpler and more reliable. Increases which were in some cases as much as three or four colours were reported consistently on the second examination.

In making a best estimate of diagnosis (item 5 in Table I), four of the five scans in the "normal group" examined twice were reported normal on each occasion. Five of the six scans from the "abnormal group", for which an examination was repeated, were given essentially the same diagnosis each time. The system is therefore consistent within reasonable limits.

The reports prepared with the tomogram will now be compared with those prepared without the tomogram for each of the parameters in turn. For one patient chosen at random the four conventional views together with the tomographic section view at 5 cm deep are shown in Fig. 1 and details of the collated results for the same patient are shown in Table IV.

TABLE III

CONSISTENCY OF TWO PARAMETERS FOR THE 16 SCANS WHICH WERE PRESENTED FOR EXAMINATION TWICE IN EXACTLY THE SAME FORM

Comparison of the two independent assessments	Same	Difference of 1 in marking	Difference of 2 in marking	Difference of more than 2 in marking
Abnormality rating	8	4	3	1
Estimated increase in colour bands above normal	11	5	0	0

This tomographic view is technically a poor example of tomography in general since motion artefacts are obvious. Only a small percentage of section scans are affected by this fault and data in Table IV show that, notwithstanding this difficulty, the section view contributed significantly to correct interpretation of the scans.

1. *Abnormality rating*

Of the 29 scans in the "abnormal group", seven were scored with the same abnormality rating with and without the tomogram. Thirteen showed a difference in abnormality rating of only one, but ten of these 13 were allocated the higher abnormality rating with the tomogram. Six scans were reported to have an appreciably higher abnormality with the tomogram (scan B/519/75 in Table IV is an example) while the remaining two were reported to have an appreciably higher abnormality without the tomogram. Twelve of the scans in the "normal group" were given the same abnormality rating with and without the tomogram (usually zero), two were rated appreciably lower with the tomogram while one was rated appreciably lower without the tomogram.

2 (a) and (b). *Position and depth of lesion*

In general the same lesion was noted both with and without the tomogram as shown in Table V. However, it is notable that for many cases in the abnormal group, ten out of 25, the lesion was not described in quite the same way at the second examination. In 15 of the 18 cases where the lesion positions were different the scans were considered to be within normal limits on one of the two examinations. Two of the four scans in the abnormal group were reported normal (*i.e.* false negative) on the conventional views but the lesion was correctly identified with the tomogram. The other two were incorrectly assessed both with and without the tomogram.

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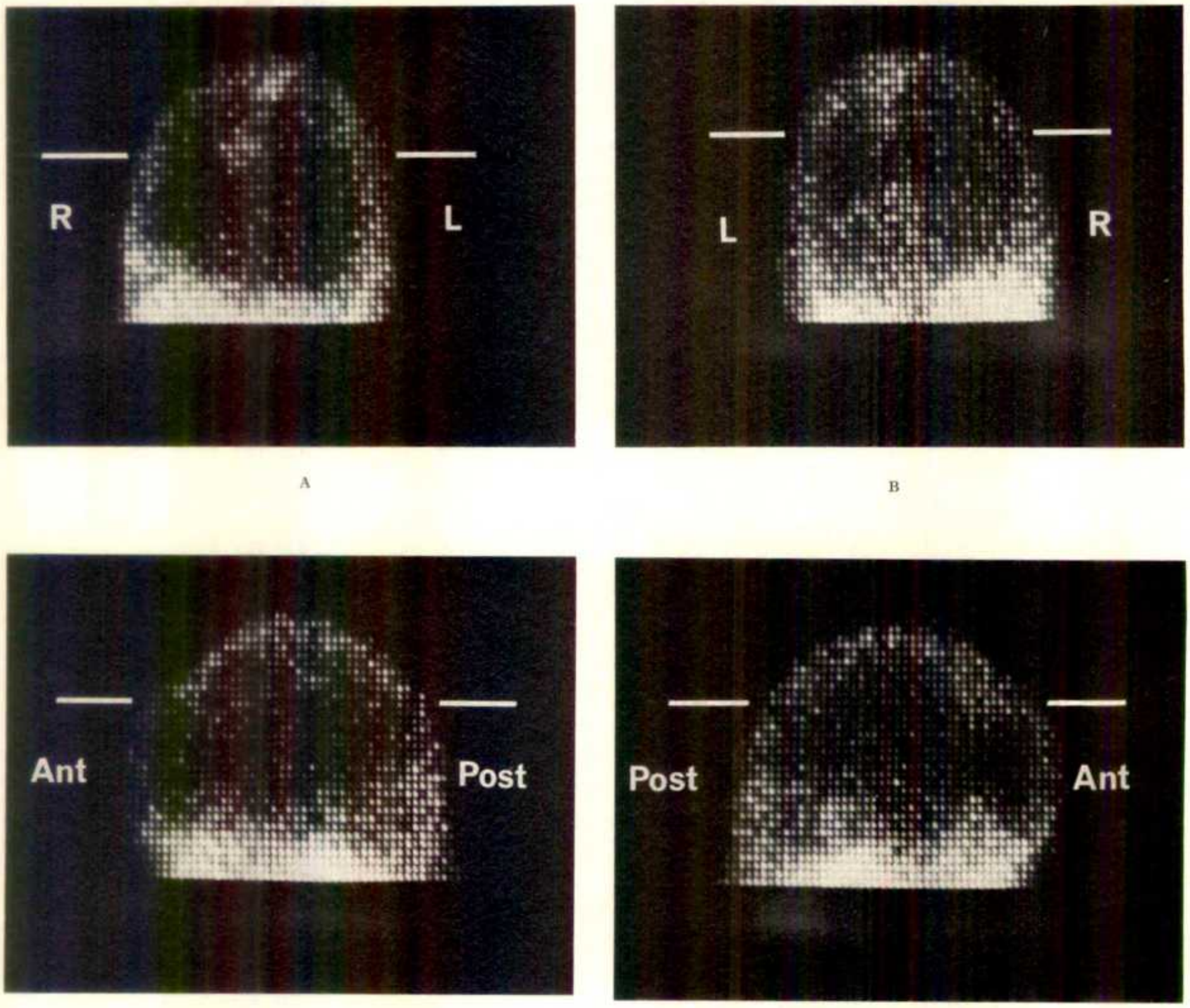

A

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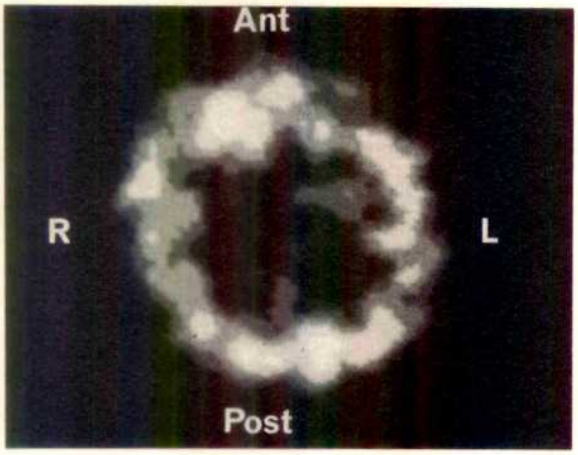
C

D



E

Fig. 1.

Grey-scale copies of conventional views and a tomographic section view for Scan No. B/519/75. The level of the tomographic section is indicated on the conventional views. (A) anterior; (B) posterior; (C) left lateral; (D) right lateral; (E) tomographic section at 5 cm where the lesion is clearly visualized as a bright area in the right anterior region. (Note that there is considerable loss of fidelity in these black and white reproductions of the original colour scans used for reporting and evaluation.)

TABLE IV

FULL DETAILS OF THE COLLATED RESULTS FOR ONE PATIENT—SCAN NO. B/519/75—PARASAGITTAL FRONTO-PARIETAL PRIMARY TUMOUR

Without tomogram (95th scan examined)	*With tomogram (30th scan examined)*	*Repeated without tomogram (123rd scan examined)*
1. Abnormality rating 1/5	1. Abnormality rating 4/5	1. Abnormality rating 2/5
2. (a) Position—frontal (b) Depth—right parasagittal (c) Shape—diffuse	2. (a) Position—frontal (b) Depth—right parasagittal 5/10 right superficial 5/10 (c) Shape—round 7/10, diffuse 3/10	2. (a) Position (i) frontal (ii) a second lesion parietal (b) Depth (i) right parasagittal (ii) left parasagittal (c) Shape (i) lobulated (ii) diffuse 5/10, surface 5/10
3. Size—2½ × 2 cm	3. Size—2½ × 2 cm	3. Size—(i) 5 × 2 × 2 cm
4. Intensity of uptake (a) Qualitatively 3/5 (b) Three colours	4. Intensity of uptake (a) Qualitatively 3/5 (b) Two colours	4. Intensity of uptake (a) Qualitatively 3/5 (b) Three colours
5. Best diagnostic estimate Single tumour 4/10 Infarct 2/10 Vascular lesion 2/10 Meningioma 2/10	5. Best diagnostic estimate Single tumour 5/10 Meningioma 5/10	5. Best diagnostic estimate Multiple secondaries 7/10 Infarct 3/10

TABLE V

A COMPARISON OF LESION POSITION

	The same	Essentially the same	Different
Abnormal group	15	10	4
Normal group	7*	1	7
Equivocal group	4	2	7

* This figure includes cases where no lesion was reported both with and without the tomogram.

TABLE VI

A COMPARISON OF BEST ESTIMATED DIAGNOSIS WITH AND WITHOUT THE TOMOGRAPHIC VIEW

	Column 1	Column 2
(a) Both estimates equally good	6	7
(b) Better estimate with tomogram	17	17
(c) Better estimate without tomogram	4	3
(d) Both estimates equally bad	2	2

Column 1—All single tumour lesions considered as one group.
Column 2—Meningioma considered as a separate category.

The results for the "equivocal group" of scans on the bottom line show that there are many scans which are extremely difficult to report consistently on scan data alone.

2 (c) and 3. *Shape and size*

These factors contributed to the final best estimate of diagnosis but have not been evaluated independently.

4. *Intensity of uptake*

(a) The qualitative estimate has not been analysed.
(b) The increase in colour bands above normal level has been analysed for the 29 scans in the abnormal group. The increase was the same with and without tomogram for eight scans and for a further 14 there was only one colour level difference. All the other seven, however, showed at least two more colours above normal in the "with tomogram" views. Since this parameter was consistent to ±1 when identical sets of scans were re-examined, these results suggest real increased sensitivity in the tomographic view.

5. *Best estimate of diagnosis*

Four results are possible for each case: (a) both estimates equally good; (b) estimate better with tomogram; (c) estimate better without tomogram; (d) both estimates equally bad. Obviously the distinctions are arbitrary, but for example "tumour 7/10, infarct 3/10" was taken to be an appreciable improvement on "tumour 5/10, infarct 5/10" for an actual tumour, while "subdural 9/10, infarct 1/10" and "subdural 8/10, infarct 2/10" for an actual subdural were scored equal.

In the first analysis, all primary or single metastatic malignancies were classed together making just four positive categories—a single primary or secondary, multiple secondaries, infarct and subdural. The results split as shown in Table VI, column 1. In the second analysis, meningioma was specified as a separate category. This resulted in a change of classification for seven cases—*e.g.* B/33/74 was a confirmed single secondary classified 8/10 single tumour, 2/10 meningioma without tomogram and 7/10 single tumour, 3/10 infarct with tomogram. It was thus moved from group (c) in the first analysis to group (a) in the second analysis. In spite of these re-arrangements, the overall distribution was virtually unaltered as shown in Table VI, column 2.

Discussion

The first point to emphasize is that it is difficult to obtain large numbers of cases where there is confirmed clinical diagnosis independent of the radioisotope scan. Although a busy department may perform 1000 or more brain scans during the year, the large majority will show no definite abnormality. The number for which the clinical diagnosis can be confirmed unequivocally by independent methods may be under 100.

Secondly, many of the positive scans are so obviously abnormal that the pathology could not possibly be missed on the conventional views even though it might not be correctly identified. This is supported by that fact that for 25 of the 29 scans in the "abnormal group" essentially the same lesion was reported both with and without the tomogram. However, two out of 29 scans in the "abnormal group" (7%) were reported normal without the tomogram, but correctly identified with the tomogram. This figure of 7% would certainly represent an appreciable reduction in the proportion of the false negative brain scans if it could be maintained. Although the small numbers involved are clearly not statistically reliable, this is also the figure found by Kuhl and Sanders (1971). Assuming a total positive pick-up rate of 10%, this would mean about seven additional positive diagnoses per 1000 brain scans.

Furthermore, in many cases where essentially the same lesion was reported, the abnormality rating was higher and the best estimate of diagnosis more accurate with the tomogram. For example, the analysis of uptake intensity by means of colour levels, item 4b in Table I, suggests that the tomographic view may sometimes display information in a more useful way than conventional views. Seven out of 29 (22%) of the scans in the "abnormal group" showed an additional two or more colour bands with the tomogram, and could consequently be reported abnormal with a far higher degree of confidence. In practice, this is probably a very considerable gain.

Reporting might be inferior with a tomographic view for several reasons. First, the tomographic section may be taken at the wrong level and this could degrade the value of the conventional views. Secondly, the information for each part of the tomographic image is collected throughout the scanning time so movement of the patient may cause distortion, as shown in Fig. 1E. Thirdly, the reconstruction algorithm might not be compatible with the collimator characteristics. Fourth, the use of too many colour levels in the display could result in false detail. Finally, it is much more difficult to identify technical errors from the appearance of the final image for tomographic than for conventional views. This possibility of inferior reporting must be considered when the information of the last parameter in Table I is analysed statistically.

The data in Table VI have been analysed by a paired sample t test. Lines a and d where the estimates are equally good or equally bad are tied pairs. Restricting attention to the $b+c$ pairs in which the two members are of different types, the null hypothesis that the tomographic view makes no difference to the diagnostic estimate gives the expectation of $\frac{b-c}{b+c}$ as zero, in other words the expectations of b and c are equal. The proportion of pairs of type b should be binomially distributed with a parameter equal to $\frac{1}{2}$. The actual figures in Table VI are different at the 1% level of significance in column 1 and at the 0.5% level of significance in column 2. We can therefore reject the null hypothesis.

These results therefore confirm statistically that, in addition to the occasional detection of a lesion not noticed on conventional views, the tomographic view improves diagnostic estimates based on radioisotope scans. For example, a section through the skull may often visualize the radioactivity in such a way that a subdural can be distinguished from an infarct or an infarct can be distinguished from a primary tumour.

Over-enthusiasm in reporting the tomographic view could increase the number of false positive reports, but there is no evidence to suggest that this occurred. Six of the scans in the "normal group" were given some level of abnormality above zero when viewed without the tomogram, while only four scans in this group were given an abnormality rating above zero when viewed with the tomogram.

One case in the "normal group" was reported consistently abnormal with and without the tomogram and essentially the same lesion was described. Closer follow up showed that these blind reports fitted

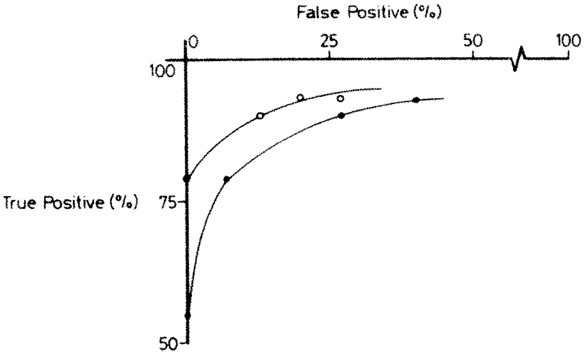


FIG. 2.

Curves showing how the percentage of true positives was related to the percentage of false positives for scan evaluations: ● without tomographic view; ○ with tomographic view.

quite well the clinical evidence of a small resolving infarct at the time of the scan even though the scan had originally been reported as normal. Thus the presence of a fairly high proportion of abnormal ratings above zero (usually one) for the "normal group" is at least partly caused by the fact that our criteria for the "normal group" could not be nearly as rigid as our criteria for the "abnormal group".

The abnormality ratings enable "receiver operating characteristics", or ROC curves, to be plotted for the two series, one with and one without the tomogram. For example, using a rating method (Green and Swets, 1966), one point on each ROC curve can be obtained by assuming that all scans with an abnormality rating of one or more are positive. The total number of true positive and false positive responses is found on the basis of this criterion and the figures are expressed as percentages of the numbers in the "abnormal group" and the "normal group" respectively. An abnormality rating of two or more is then taken to indicate a positive response, and the procedure is repeated to obtain another point on each curve.

No scans in the normal group were accorded an abnormality rating of four or five, so when four is the minimum abnormality level for the scans to be scored positive, both points lie on the axis. No further information can then be obtained by taking five as the minimum abnormality level so these points have not been plotted. As can be seen from Fig. 2, an increase in true positive response was obtained at all false positive response levels when the tomogram was included.

In conclusion, this analysis of a small number of cases provides evidence that transverse axial emission tomography makes a useful contribution to the accuracy of radioisotope brain scan reports. We propose to use the experience gained in this pilot study to plan a prospective clinical trial.

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^{99}Tc^{m}-diphosphonate scanning as an aid to diagnosis of infection in total hip joint replacements

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Abstract

Local infection following total hip joint replacement is often difficult to diagnose. Bone scanning with ^{99}Tc^{m}-diphosphonate has been used in an attempt to detect such infection by assessing uptake of ^{99}Tc^{m} in the hip. Posterior view dot scans of patients with total hip joint replacements were analysed quantitatively to determine the ratios of dots in regions around the acetabular, trochanteric and femoral parts of the prosthesis compared with normal bone. The scans were also assessed visually. Patients with definite evidence of infection showed higher uptake than control patients. The clearest distinction in uptake between the two groups was in the femoral shaft region. The data from these two groups of patients were used to propose diagnostic criteria for detecting abnormalities on scans. These criteria were applied to scans of a third test group of patients who had painful hips, but no definite evidence of infection. The numerical method of analysis is less subjective and may therefore be preferable as a means of providing evidence for or against a diagnosis of infection in patients with painful hip replacements.

Infection of a total hip joint replacement may be caused by an organism introduced at the time of surgery, but often it does not become apparent until much later. For example, in one series of patients in whom infection was diagnosed by clinical findings, radiographs and blood tests, 15% of the diagnoses were not made until between one and two years after operation, and 23% after more than two years (Charnley, 1972). Earlier diagnosis may be aided by observing the uptake of a bone-seeking radiopharmaceutical in bone around the prosthesis. A method has been described using ^{85}Sr, external counting and scanning (Bauer *et al.*, 1973). Since ^{99}Tc^{m}-phosphate compounds are now more widely used for bone scanning, one of these radiopharmaceuticals has been investigated as an aid in diagnosing infection in patients with pain following total hip joint replacement. Scans were evaluated quantitatively to establish diagnostic criteria for distinguishing between normal and abnormal results.

Patients

Twenty-seven patients with a total of 34 replacement hip joints were scanned at an interval of between three and 75 months after operation. Three of the patients were scanned on two occasions, the rest only once. All patients had Charnley prostheses which had been inserted with osteotomy of the great trochanter, except for four of the patients in the control group who had Muller prostheses inserted without trochanteric osteotomy.

The patients were classified in three groups according to the following post-operative criteria:

Group 1. Controls (14 hips)

Patients in this group had no significant post-operative pain or radiographic abnormalities in the treated hip. Five patients had contralateral painful hips which were classified in Groups 2 or 3.

Group 2. Manifest infection (7 hips)

Patients in this group fulfilled one, or more, of the following conditions:

1. A discharging sinus at the operation site.
2. An organism grown from tissue specimens from subsequent re-operation.
3. Continuous pain, both at rest and on weight bearing, erythrocyte sedimentation rate (ESR) greater than 40 mm/h (normal range 5–15 mm/h) and radiographic evidence of infection (progressively larger localized radiolucency around the prosthesis greater than 2 mm in width developing later than six months after operation).

Specimens obtained from a sinus or at operation from all except one of these patients grew organisms (*Staphylococcus epidermidis* or *Staphylococcus pyogenes*). The only exception had continuous pain, an ESR of 42 mm/h and radiographic evidence suggesting infection. All the patients in this group received antibiotics for varying periods after the development of pain, and before their scan. In all cases, the known site of infection was around the femoral component.

Group 3. Pain without manifest infection (13 hips)

Patients in this group had post-operative pain either continuously or only on weight-bearing. Although some patients had an abnormal ESR or radiograph, none had, at the time of this study, sufficient evidence of infection to be included definitely in Group 2.

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METHOD

Four hours after an intravenous injection of 15 mCi ^{99}Tc$^{\mathrm{m}}$-labelled 1-hydroxy-ethylidine-1, 1-disodium phosphonate (HEDP) (Castronovo, 1974), the patients' hips were scanned using a 1.27 cm detector scanner (Picker 500D) fitted with focused collimators (type 2114B, 7.5 cm focal length, 1.3 cm resolution). The pulse height analyser window was 126–170 keV. The maximum area which could be scanned with this instrument was just sufficient to include the whole hip prosthesis and a portion of the lower lumbar spine. The hip joint was most clearly seen on the posterior view which was chosen for quantitative analysis. With the aid of a post-operative radiograph four regions were marked on the photoscan (Fig. 1), corresponding to the acetabulum (A), neck of the prosthesis region (B), trochanteric (C) and shaft portions (D) of the prosthesis and surrounding femur. There was some variation in the size of each region between patients because of anatomical differences, but this variation was small. A region of constant area (4×4 cm) in the lower lumbar spine (E) showed the most constant uptake on all the scans, and was therefore used as a standard of normal bone uptake in each patient. The outlines of each region were transferred to the paper dotscan and relative uptakes of radioactivity were estimated by counting the dots within them. The dot scaling factor was such that separate dots could be distinguished. Counting was aided by use of a hand tally counter. The tissue background contribution was estimated from a part of the scan (F) representing soft tissue in the thigh. After appropriate scaling according to the ratio of the areas of the regions (easily calculated, since the regions were all of simple geometrical shape) the background contribution was subtracted from the number of dots in each delineated region. The net number of dots in each region, divided by the number in the region (E) representing normal bone, was called its "uptake ratio".

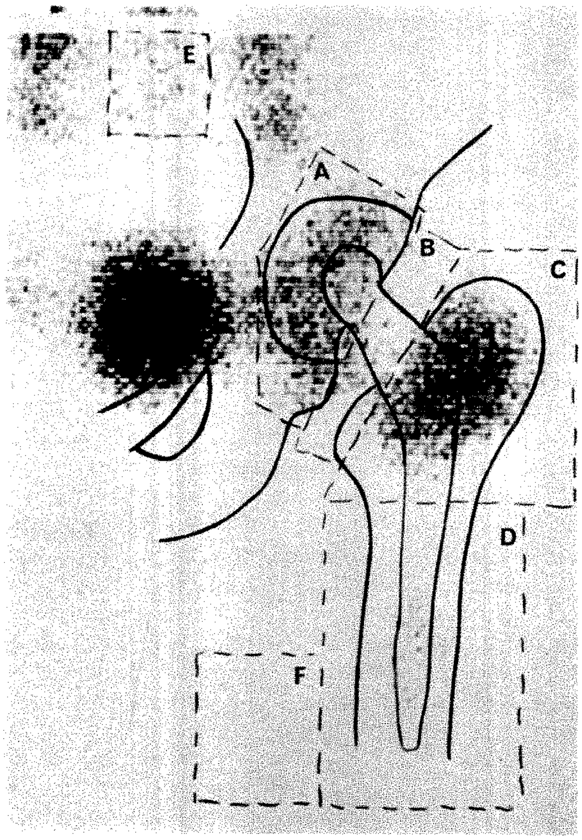

FIG. 1.

Posterior photoscan of right hip with outlines of bone and metal prosthesis traced from radiograph. Broken lines show location of regions used for calculation of activity ratio: acetabulum (A), neck of prosthesis (B), trochanteric (C) and shaft (D) portions of prosthesis and surrounding femur, normal bone (E), soft tissue (F).

The photoscans were also assessed visually without knowledge of the patient's classification and the uptake in each region was given a score on the following scale: no uptake, 0; slight uptake, 2; uptake less than vertebrae, 4; equal to vertebrae, 6; equal to sacroiliac joints, 8; greater than sacroiliac joints, 10.

The uptake ratios and visual scores were both summed separately for each hip to provide in addition an expression of the total uptake of ^{99}Tc$^{\mathrm{m}}$ in the whole hip joint.

RESULTS

Group 1. Controls

At less than nine months after operation the ratios for the whole hip, and for regions C and D (Table I, Group 1 (a)), were significantly higher than those found later (Group 1 (b) ($P < 0.05$, Wilcoxon's Rank Sum Test).

There was no further variation with time after nine months. Uptake ratios were comparable for patients with Charnley and those with Muller prostheses, so no distinction has been made between these patients.

Group 2. Manifest infection

All patients in this group were studied at more than nine months after operation. The uptake ratio

TABLE I

Uptake in regions of the hip

Group	Number of hips		Time after operation, months	Uptake ratio					Visual score				
				A	B	C	D	Sum	A	B	C	D	Sum
1. Control patients													
(a) ⩽9 months after operation	7	*mean*	5.7	1.7	0.5	2.0	1.2	5.5	4	1	5	3	13
		range	3–9	0.9–3.2	0.3–1.0	0.9–2.6	0.8–2.0	3.7–6.9	2–6	0–4	2–8	0–4	8–18
(b) >9 months after operation	7	*mean*	25.3	1.4	0.4	0.4	1.0	3.2	2	1	2	1	6
		range	10–49	0.9–2.6	0.2–0.6	0.5–1.7	0–0.9	1.65–5.7	2–4	0–2	2–3	0–2	4–9
2. Patients with manifest infection	7	*mean*	45.4	2.5	0.7	2.4	3.0	9.0	6	3	6	7	25
		range	15–75	1.9–3.7	0.5–1.3	0.7–5.0	1.8–4.6	6.6–2.2	2–8	0–8	4–10	4–10	20–30
3. Patients with painful hips													
(a) ⩽9 months after operation	5	*mean*	5.4	2.0	0.5	3.0	1.5	7.1	4	0	8	4	16
		range	4–9	1.2–2.9	0.4–0.7	2.0–4.1	1.0–2.6	5.7–10.0	2–7	0–1	6–10	2–7	10–22
(b) >9 months after operation	11	*mean*	25.0	1.7	0.5	2.0	1.0	5.3	4	1	5	3	12
		range	11–52	0.9–3.5	0.3–1.0	0.8–6.0	0.3–2.6	2.7–13.1	2–6	0–3	2–8	0–6	4–44

Key to regions: A – Acetabular; B – neck of prosthesis; C – trochanteric; D – shaft portion of femoral prosthesis.

for each region on scans of patients with manifest infection was higher ($P < 0.05$) than in the corresponding control group (1 (b)). The difference between the groups was most marked in the femoral shaft region (D) ($P < 0.001$).

Group 3. Pain without manifest infection

This group of patients was sub-divided in the same way as the control group, into those scanned at up to nine months after operation (3 (a)) and those scanned later (3 (b), Table I). The uptake ratios in Group 3 (a) were similar to those in the control Group 1 (a), except for the trochanteric region (C), where the ratios for the patients with pain were significantly higher ($P < 0.05$) than for the controls. Eleven hips were scanned at more than nine months after operation, including three which had also been scanned at less than nine months. The results for this group overlapped the ranges for both the infected and corresponding control groups, and were significantly different from neither.

Diagnostic levels

The control and abnormal ranges represented by data from scans of hips in Groups 1 (b) and 2 respectively overlapped to a small extent. Discrimination between normal and abnormal results was therefore proposed by means of diagnostic levels of the uptake ratio and visual score for each hip region. These were selected to minimize the proportion of false diagnoses (Armitage, 1971) which would be made when using the uptake ratios to assess the scans of these patients. These diagnostic levels (Table II) must be equalled or exceeded for a scan to be considered abnormal. They apply only to scans at more than nine months after operation.

The diagnostic levels of the hip joint uptake were used to assess the scans of Group 3 (b) patients whose diagnosis was uncertain. In three cases the scans could be classified as abnormal in all regions of the hip according to the uptake ratio, and in three others all parts of the scan were normal. The rest of the scans gave abnormal results for some of the regions. The visual score diagnoses were in general agreement with those for the uptake ratio.

DISCUSSION

Bone scanning is more sensitive than radiography for detecting sites of high metabolic activity, including infection (Staheli *et al.*, 1972), because uptake of tracer at the affected site can be observed before sufficient change in the bone structure has occurred to be visible on a radiograph (Galasko, 1972).

TABLE II

DIAGNOSTIC LEVELS FOR HIP JOINT UPTAKE

Region	A	B	C	D	Sum
Diagnostic level of uptake ratio	1.7	0.5	1.2	1.0	5.8
Percentage of scans in Groups 1 (b) and 2 correctly classified	92	93	86	100	100
Diagnostic level of visual score	5	3	4	3	10
Percentage of scans in Groups 1 (b) and 2 correctly classified	92	86	100	100	100
Percentage of Groups 3 (b) scans showing agreement between activity ratio and visual score classification	82	64	73	64	73

Increased uptake of ^{99}Tc^{m}-HEDP at the site of osteogenesis (Castronovo and Callahan, 1972) may be expected during normal healing following bone surgery and total hip replacement. When the bone is healed, uptake should decrease. If a high rate of bone turnover should continue because of local infection, fracture, failure to heal or new bone formation (Bauer, 1975) the expected fall in tracer uptake will not occur. We observed a high uptake of ^{99}Tc^{m} in hips of the control group scanned within nine months of surgery. After that, uptake was lower and showed no further change with time. A similar finding was reported in studies using ^{85}Sr (Bauer *et al.*, 1973).

The replacement hip joint scan, therefore, represents a difficult problem for interpretation, since the contralateral joint does not provide a suitable reference for visual comparison unless it also contains a symptomless replacement of similar age. Some other method of classifying the scans is therefore appropriate.

Since no patient with manifest infection was scanned less than nine months after operation, we cannot say whether an abnormally high uptake would be expected in such patients during this period. However, both the uptake ratio and the visual score gave a clear distinction between control and infected hips in patients scanned more than nine months after operation. The diagnostic criteria established by comparing these two groups were used to evaluate the borderline patients in Group 3 (b). In this group, the diagnoses on the basis of uptake ratios and visual scores did not always agree, but this is not surprising since these were also the patients in whom an accurate clinical diagnosis by other means is the most difficult. On the basis of the diagnostic criteria in Table II, three of the 11 patients in Group 3 (b) appeared to have strongly suggestive evidence of occult infection, and three others seemed unlikely to be infected. The test appears to provide little guidance in the other five cases.

It must be noted that increased uptake of ^{99}Tc^{m}-HEDP can be due to causes other than infection, such as fracture or ectopic bone formation, but these are usually detectable on a radiograph and were not applicable here. Loosening of the prosthesis without local infection may cause pain but be undetected radiographically. Unfortunately, we have not been able positively to identify any patients in this category and so cannot say whether normal or increased uptake is to be expected in such cases. The uptake ratio method has the advantage over visual assessment of being independent of subjective factors in the photoscan display. Although the method of analysis described is tedious if facilities for automatic data collection and processing are not available, such refinements would make the numerical assessment simple. A measurement of the absolute uptake of tracer in the hip might give better results, but such a measurement would be very difficult owing to high attenuation of the ^{99}Tc^{m} radiation in bone and the metal prosthesis.

We conclude that a quantitative evaluation of hip joint scans enables a proportion of them to be classified as normal or abnormal, and can thus provide supporting evidence for or against a diagnosis of infection.

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Book review

Advances in Picture Reconstruction—Theory and Applications. Edited by Z. H. Cho. "Computers in Biology and Medicine", Volume 6, number 4, October, 1976. Special issue, pp. 136, £8·25. (Oxford, Pergamon Press).

In recent years there has been an explosion of interest in three dimensional image reconstruction from projections. The timely appearance of this special issue is a welcome introduction to this vast subject and is primarily intended for the mathematical physicist. The newcomer might well begin with this collection of papers which not only reviews in some detail the theoretical foundations but clearly directs the reader to the wealth of literature which has accompanied the translation of reconstruction techniques from the realms of electron microscopy and radioastronomy to that of diagnostic radiology. Papers by Mersereau on direct Fourier transform techniques, by Herman, Lakshminarayanan and Naparstek on convolution algorithms and the discussion of iterative reconstruction by Herman and Lent are central to this volume. A sensible comparison of the performance of commercial computerized transverse axial tomographic (CAT) machines relies on an understanding of the different philosophies of these algorithms, and who better to discuss them than these authors who have figured most prominently in their development. Mersereau discusses the limitations of sampled data and finite number of views in terms of Fourier space interpolation schemes. In presenting their discussion of the formally equivalent convolution algorithm, Herman *et al.* stress its appropriateness to real time imaging. They rederive the mathematics of fan beam reconstruction without the need to invoke the concept of ray reordering and illustrate fan beam convolution by reconstructing a dog's thorax from 120 views. Herman and Lent demonstrate that the iterative techniques, particularly appropriate with noisy, high contrast or incomplete data, all reduce to some quadratic optimization problem. Their paper is particularly useful as they choose to answer their critics and compare iterative and Fourier techniques in four ways, namely cost of computing, accuracy, availability of supporting theory and applicability. The result is a happy compromise; no method wins on all counts.

The choice of supporting papers must have been difficult for the editors: there are still so many controversial aspects of reconstruction tomography. The inclusion of a paper by Barrett, Gordon and Hershel aiming to summarize the quantum statistical limitations succeeds in deriving useful rule of thumb expressions relating spatial and density resolutions, signal to noise ratio and dose. Furthermore, no introductory volume would be complete without a discussion of energy dependent reconstruction and Macovski clearly demonstrates the techniques for adapting algorithms for polychromatic X ray sources. It is a pity that in Ledley's introduction to computerized tomography he concentrated too heavily on one commercial device, the ACTA scanner. If the early '70s are remembered for the awakening of diagnostic radiologists to the potential of CAT, the latter part of the decade will be recalled for the mushrooming of commercial devices. It is surely an omission that here we find no intercomparison.

Finally we are introduced to positron emission tomography (PET) which seems destined to succeed where gamma emission tomography is in difficulties. Hoffman and Phelps explain how the relative constancy of the line spread function with depth overcomes the problems of reduced resolution and sensitivity inherent in gamma emission. The last two papers in this volume summarize what factors at present limit PET, but it seems clear that the role of positron cameras for dynamic studies in nuclear medicine will become equally important to that of transmission devices for static imaging.

The editor's disclaimer that this special issue may not encompass all the recent developments in three dimensional image processing is overmodest. It succeeds in both providing a reference text and bringing the reader to the forefront of the subject within the relatively short space of ten well constructed papers.

STEVE WEBB.

1977, *British Journal of Radiology*, *50*, 567–572

Re-irradiation of rat tails to necrosis at six months after treatment with a "tolerance" dose of X rays or neutrons

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Abstract

Rat tails were re-irradiated to necrosis levels at about six months after various fractionated treatments with 290 kV X rays or 14 MeV neutrons. The X ray dose required to produce necrosis in half of a group of tails (ND_{50}), which had been heavily X-irradiated six months before, was 91 ±4% of the ND_{50} for aged controls. After prior neutron-irradiation, however, this value was 87 ±4% (neutrons in second treatment) or 75 ±5% (X rays in second course).

The "effective" oxygenation of mouse tails at this time after X-irradiation was similar to that of controls; thus these percentage dose values indicate the remarkable tolerance of this organized tissue to a second course of X-irradiation, and the presence of more residual injury in neutron-irradiated tissues.

Long-term residual damage in irradiated normal tissues is recognized as important regarding continued tissue function and the effect of re-treatment. The general clinical view appears to be that a second treatment should be avoided, but if it *is* considered necessary the tolerance dose for re-irradiation will be lower than that for a first treatment, by an amount which depends on factors such as the interval of time between treatment courses, the treatment site and volume, the previous dose and the functional state of the tissue. In order to investigate quantitatively some aspects of residual damage, the retreatment of rat tails to necrosis after various initial neutron or X-ray fractionation schedules was investigated with regard to (a) radiation dose in the first course, (b) length of fractionation schedule in the first course, (c) radiation quality in the first and second courses, and (d) changes in "effective" tissue oxygenation after a first treatment.

Materials and Methods

Female outbred Wistar rats or female $B2D6F_1$ mice were used where stated. Details of the irradiations and assay technique have been given previously (Hendry *et al.*, 1976). Briefly, a nominal 3 cm length of mid-rat-tail was irradiated with either 14 MeV neutrons (75 rad min^{-1}) or 290 kV X rays (250 rad min^{-1}), and the dose was estimated for necrosis of the tail by ten weeks post-irradiation in half of a group of rats (the ND_{50}). The rats had been irradiated previously (Hendry *et al.*, 1976) with various fractionation schedules of either X rays or neutrons (detailed below), and in all cases the doses in the first course were within ±20% of the ND_{50} for each treatment. The rats whose tails were not necrotic following the first treatment were re-irradiated about six months later (extreme range five to seven months), and all pre-irradiated rats (and control rats of the same age) were given four daily fractions of either X rays (4FX) or neutrons (4FN). Sufficient rats were available for pre-X-irradiated or pre-neutron-irradiated rats to be retreated by either type of radiation, and in two instances low fraction numbers (1 and 2F) were distinguished from high fraction numbers (4, 8 and 16F) in the first course. In all cases, pre-irradiated rats were randomized among the groups given re-treatment.

The rats to be retreated had received different doses in the first course. The mean dose given in the first course to those animals receiving two courses of X rays (X+X) was 1.06 times the first course ND_{50}, the extreme range being 0.92 to 1.17 times the ND_{50}. For those receiving a first course of X rays followed by a second course of neutrons (X+N), the mean dose given in the first course was 0.95 times the ND_{50} (extreme range 0.94 to 1.10). For successive courses of neutrons and X rays (N+X) the mean dose was 0.89 times the ND_{50} (range 0.85 to 0.99), while for successive doses of neutrons (N+N) the mean dose was also 0.89 ND_{50} (range 0.85 to 0.98). Thus the pre-X-irradiated rats had received, on the average, about an ND_{50} dose, whereas the pre-neutron-irradiated rats had received 0.89 ND_{50} (on average). This is about ND_{10}, which can be considered an upper limit to the tolerance dose in this system (Hendry *et al.*, 1976). These differences in dose are considered below.

For mice, a 2 cm length of mid-tail was irradiated with single X-ray doses (430 rad min^{-1}), with the tail surrounded by air, oxygen, or nitrogen with a tail clamp (Hendry *et al.*, 1976). The irradiations were performed at about six months (extreme range four

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*We record with regret that Dr. Stewart died at the end of March.

TABLE I

ND_{50} VALUES FOR RATS' TAILS AFTER TWO COURSES OF TREATMENT

Course		ND_{50} (rad)	ND_{50} ratio*	Reaction at ND_{50}†	
First	Second at six months			Peak	Average
		4FX			
4FX	0	7040±80	0.93±0.03	2.0±0.4	1.7±0.3
0	4FX	7610±220	1.0	2.3±0.3	1.9±0.2
1–16FX	4FX	6950±180	0.91±0.04	2.4±0.2	1.7±0.2
1–16FN	4FX	5700±320	0.75±0.05	2.1±0.3	1.8±0.1
		4FN			
4FN	0	2980±50	0.96±0.04	2.3±0.2	1.9±0.2
0	4FN	3120±120	1.0	2.5±0.3	2.0±0.3
4–16FX	4FN	2880±70	0.92±0.04	2.3±0.1	1.8±0.1
1–16FN	4FN	2720±60	0.87±0.04	2.4±0.2	1.9±0.2

ND_{50} values are given as total dose to nearest ten rad.
4FX then 0. Controls irradiated with four daily fractions of X rays at the time of the first course only (from Hendry *et al.*, 1976).
0 then 4FX. Controls irradiated at the time of the second course only (no pre-irradiation).
1–16FX then 4FX. Pre-treatment with a range of X-ray fractionation schedules.
1–16FN then 4FX. Pre-treatment with a range of neutron fractionation schedules.
Similarly for irradiation by four daily fractions of neutrons (4FN) after various pre-treatments (bottom half of table).
Standard errors quoted on ND_{50}'s; standard deviation on reactions.
*Ratio of the ND_{50} for the specified paired course with respect to that for 4FX alone in the second course (upper half of table) or 4FN alone (lower half of table).
†See text.

to seven months) after the initial treatments with one to 15 daily fractions (to be published). Dose levels in the first course were designed to bracket the ND_{50}, and thus the average dose received by the re-treated mice in the first course of treatment was, as with the rats, about a tolerance dose.

RESULTS

Rat tails

Probability curves of the proportion of tails showing necrosis as a function of dose are shown in Fig. 1 for a second course of neutrons (left of figure) or X rays (right of figure). Data from repeat experiments at each dose level were pooled. Best-fit lines are drawn, calculated by a weighted regression analysis using the probit computer program described by Gilbert (1969). The different irradiation regimens used are detailed in Table I. ND_{50} values and ratios to the ND_{50} for a single course of treatment are shown in Table I, together with the peak and average reaction levels (13 to 57 days after the last fraction) which resulted in 50% necrosis, calculated as described previously (Hendry *et al.*, 1976). The effect on ND_{50} of six months of ageing, shown in lines 1 and 2 of Table I for X rays and in lines 5 and 6 for neutrons, is marginal (4–7%). The reduction in ND_{50} caused by prior X-irradiation (lines 3 and 7, Table I) is only 8–9%. More marked however is the effect of previous neutron-irradiation (lines 4 and 8, Table I), where the ND_{50} is reduced by about 25% (X rays in second course) or 13% (neutrons in second course). There is a trend toward a higher probit slope for rats previously irradiated with neutrons (Fig. 1). This means that the dose would have to be reduced more after neutrons to cause a tolerance level of damage (ND_{10}), but the effect is not significant on these data.

Peak and average reactions in the second course are similar for all prior treatments (Table I), but the general trend is compatible with that noted previously for the first course (Hendry *et al.*, 1976), namely slightly higher reactions with neutrons than with X rays at the ND_{50}.

The re-treated rats were randomized with respect to the dose given in the first course of treatment and a detailed analysis was made of the dependence (for each rat) of the response of the tail as a function of the dose given in the first course of treatment. For each of the four combinations of first and second treatment, *i.e.* X+X, N+X, X+N, N+N, the mean fraction of necroses for all rats irradiated in each second course was compared both with the fractions of necroses for rats treated in the first course with doses *less* than ND_{50}, and for rats treated with doses *more* than ND_{50}. Although individual combinations of treatments usually contained fewer rats than needed for a good statistical treatment, the combined analysis for the 217 rats

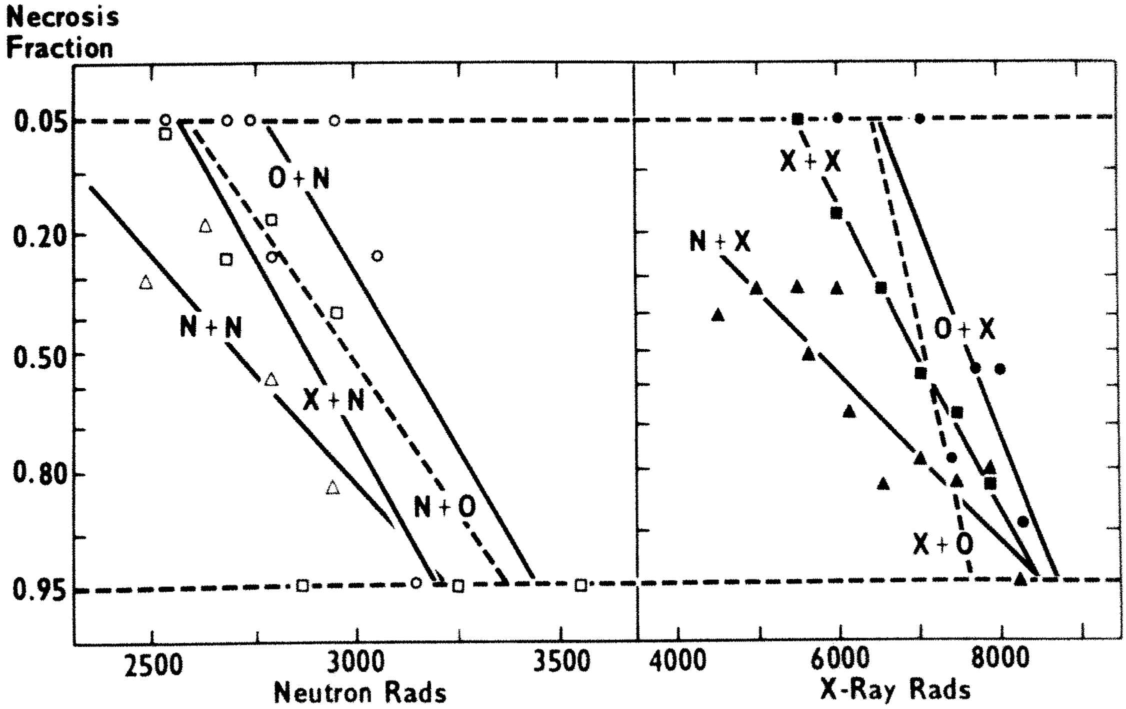

FIG. 1.

Probability curves for necrosis as a function of total neutron or X ray dose delivered in four daily fractions. Necrosis fractions of 0 or 1 shown on 0.05 and 0.95 levels respectively for convenience. Letters given on lines correspond to those given in columns 1 and 2 of Table I, with fraction numbers omitted for clarity. Dotted lines are (N+0) or (X+0), taken from Hendry *et al.* (1976). Open circles (0+N); closed circles (0+X). Open squares (X+N); closed squares (X+X). Open triangles (N+N); closed triangles (N+X).

retreated in the four paired schedules taken together showed identical necrosis fractions of 0.53 both for the previously underdosed rats (88/166) and the previously overdosed rats (27/51).

A similar analysis was made of the dependence of ND_{50} at re-treatment on the number of fractions used in the first course. In two schedules, X+X and N+N, rats given a large number of fractions in the first course showed a slightly higher ND_{50} following the second course than did rats previously given few fractions. The difference between four, eight or 16 fractions on the one hand and one or two fractions on the other was 6–7% both for X+X and N+N, and was not statistically significant. The mean dose given to the rats in the first course was greater for those animals receiving a higher number of fractions, being 1.13 ND_{50} for high numbers of X ray fractions as compared to 0.93 ND_{50} for a low number of X ray fractions. The corresponding values for animals given a first course of neutrons were 0.92 ND_{50} for high numbers of fractions and 0.86 for low numbers. However, in neither case would variations of this magnitude affect the response to re-treatment (see previous paragraph).

The quantal nature of this necrosis assay makes it possible to assess not only the reduction in dose necessary on re-irradiation, but also the increase in necrosis fraction can be estimated when the previous treatment is not taken into account. The latter information has been derived from Fig. 1 and is presented in Table II. The increase in necrosis fraction (comparing column 2 with column 4) is shown when similar ND_{10} or ND_{50} doses are delivered a second time. The increases are larger (values in parentheses) when the change in sensitivity with age of control rats is taken into account, and they are more pronounced after previous irradiation with neutrons.

Induction of tumours in rats

X-irradiated rats received an average whole-body dose of less than 1% of the dose to the tail, and the tumour incidence rate in such rats was minimal (2% to date). However, neutron-irradiated rats received a much greater average whole-body dose of about 15% of the dose to the tail, this being lower at the head (about 10%) than at the rear (about 20%), as described previously (Hendry *et al.*, 1976). The dose to

TABLE II

INCREASE IN ND_{10} AND ND_{50} PRODUCED BY RE-IRRADIATING WITH THE SAME DOSE (OR ITS EQUIVALENT) AS REQUIRED IN THE FIRST COURSE FOR ND_{10} OR ND_{50}

First course	Second course	Necrosis fraction	Estimated first course dose (rad)*	Repeated dose (rad)	Approximate resulting necrosis fraction
X	X	0.1	6570 X	6570 X	0.33 (0.42)†
		0.5	7040 X	7040 X	0.53 (0.75)
N	X	0.1	2670 N	6570 X	0.70 (0.73)
		0.5	2980 N	7040 X	0.78 (0.86)
X	N	0.1	6570 X	2670 X	0.14 (0.44)
		0.5	7040 X	2980 N	0.69 (0.89)
N	N	0.1	2670 N	2670 N	0.44 (0.68)
		0.5	2980 N	2980 N	0.80 (0.89)

*Dose values taken from Table II in Hendry *et al.* (1976).

†Values in parentheses calculated using the dose values pertinent to *aged* controls *i.e.* using the reference lines 0 + X and 0 + N in Fig. 1 (and corresponding ND_{50} values in Table I) instead of lines X + 0 and N + 0.

TABLE III

MOUSE TAIL ND_{50} DOSES AND DOSE RATIOS FOR SINGLE FRACTION X-IRRADIATIONS

Tail environment	Hendry *et al.*, 1976		Second course	
	First course			
	ND_{50} (rad)	Ratio.†	ND_{50}* (rad)	Ratio.†
N_2 + clamp	6818 ± 158	1.0	6260 ± 100	1.0
Air	4418 ± 42	1.54 ± 0.04	3940 ± 70	1.59 ± 0.04
O_2	3356 ± 55	2.03 ± 0.06	3840 ± 110	1.63 ± 0.05

Standard errors quoted.

*Quoted to nearest ten rad.

†Ratio of dose for specified tail environment to that for N_2 and clamp.

the whole body was thus about 450 rad of neutrons. Only two rats in the whole series died before necrosis was assayed, but tumour induction was pronounced, occurring so far in about 20% of the survivors of those combined schedules in which neutrons were given for the first course of treatment. The tumours have been solid tumours, palpable from about seven months after the first course of treatment, *i.e.* at about 11 months of age onwards, and from about two months after treatment when neutrons were used for the first time in the second course or as aged controls, *i.e.* at about 12 months onwards. The data were insufficient to correlate tumour incidence with dose or with fractionation schedule, and no comparison is available with the incidence rates of X-ray induced or spontaneous tumours from these experiments. Of 29 tumours examined histologically, five were classified as sarcomas, eight adenocarcinomas, four benign fibrous lesions, two adenomas, and ten mammary hyperplasias. Other published work on tumour induction after X rays or neutrons has shown that the above incidence rate after neutrons is unlikely to be due to a high RBE for this effect at these dose levels *e.g.* Shellabarger (1976). Following the first course of radiation it was noted (Hendry *et al.*, 1976) that a small proportion of healed tails deteriorated, after scoring at ten weeks, to necrose by six months, *i.e.* at the time of re-irradiation (4% after X rays, 8% after neutrons). These proportions were not markedly different after re-irradiation, at 3% overall, although this is a lower limit due to the gradual loss of animals from tumour production.

Mouse tails

ND_{50} values for mouse tails (single X ray doses) under different environmental conditions are shown in Table III, which compares values for a second irradiation with published values for a first irradiation. The latter are taken from Hendry *et al.* (1976). The reduction in ND_{50} of rat tails on re-treatment with four daily fractions is again observed here for mice with single doses, the values being 11% (air) and 8% (N_2 + clamp). Also demonstrated is the similarity in "effective" oxygenation of the target tissue for the first or second irradiation as shown by the ratios of doses needed with N_2 and clamp to air. An unusual feature on re-irradiation is the much reduced sensitization produced by flowing oxygen round the tail at the time of irradiation, indicating that there is a marked loss of ability to take up oxygen through the skin in the pre-irradiated animals.

DISCUSSION

Residual damage to normal tissue can be assessed experimentally by functional assay or by the dose required at re-treatment. For example, residual radiation damage has been reported in haemopoietic tissue (Baum and Alpen, 1959; Hendry and Lajtha, 1972), and this has been found to be greater after high than after low LET radiation for equivalent initial damage (Hendry *et al.*, 1974). In other systems, a reduction in long-term repair of damage has been indicated after neutron irradiation. For example, there is a lack of chromosomal repair in mouse liver (Curtis and Tilley, 1965), and a lack of "slow repair" in mouse lung (Field and Hornsey, unpublished) as measured by 40–180 day death (in contrast to an earlier indication by Field *et al.* (1976).

The reduction of ND_{50} on re-irradiation with X rays at six months after a previous treatment with X rays, amounting to about 10% for the tails of both rats and mice, is compatible with previous findings of about 10% for early skin reactions in mouse legs (Denekamp, 1975) and of 0–15% estimated for the same test by Brown and Probert (1975). It is also not very different from the finding by Field and Law (1976) of no reduction in the case of rats' ears. For rat tails, the reduction of dose would be similar irrespective of the endpoint used, *e.g.* necrosis fraction, peak or average early reaction (Table I). All the above reductions in X ray dose are in contrast to those of 17% to $\geqslant 35\%$ for late deformity in mouse legs (Brown and Probert, 1973, 1975). Possible reasons for this have been discussed in terms of different target tissues (Brown and Probert, 1975). More recent data have not confirmed such an effect in the case of deformity of rat ears (Field and Law, 1976).

Although reductions in dose are small on re-irradiation with X rays to give the same level of damage (Table I), reductions of this order produce marked differences in response (Table II) due to the steepness of the dose-response curves (Fig. 1). Also, the higher incidence of necrosis on re-irradiation to the same dose levels (Table II) is somewhat masked by the increasing radioresistance of control tails with age. The tails to be re-irradiated were a selected group, in that they had not necrosed following the first course of radiation. The selected tails may be expected to be the more radioresistant ones, and this could tend to mask any residual damage in the population as a whole. However, the comparison of response to re-irradiation of previously underdosed and overdosed tails, where such selection was small and large respectively, produced no disparity in response.

Published clinical evidence on response to re-irradiation is scarce, and some further clinical observations are presented in the following paper. As the principles of such treatments are not generally established, the use of the partial tolerance formula described by Ellis (1968) is considered here as a possible guide for this situation. The formula attempts to adjust doses for the time gap in split schedule treatments. For gaps greater than 100 days the effect of time is assumed to have become constant, based on the time when histological recovery of rectal vascular and connective tissue damage was complete (Ellis and Sorensen, 1974). According to the formula, the reduction in partial tolerance after this time depends almost entirely on the overall time of the initial fractionation schedule, and it is calculated to decrease from 0.4 for single doses to about 0.2 for 16F/22 days, *i.e.* less extra dose is needed to reach tolerance after pre-treatment with longer fractionation. The present work is inconclusive on this point, but the trend is the other way, with slightly higher ND_{50} values after pre-treatment with high numbers of fractions. Also, there is a much greater decay of damage (or less residual damage) than predicted between the first and second treatments. Such disparities could be accounted for by the inapplicability of the formula for radical re-treatments, or by the unsuitability of this model system for deriving general radiotherapeutic principles concerning response to re-treatment. The former requires more evidence; the latter must be considered in the light of the constitution of the tissue. Although the target cell population for tail necrosis is unknown at present, *all* tissue elements critical to the continued function and structural integrity of the irradiated section and of the unirradiated distal tail tolerate these dose levels at re-irradiation within the time limits of the present assay.

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Book review

Principles of Radiation Therapy. By Thomas J. Deeley, pp. 159, 1976 (London, Butterworth Group), £4·95.

This short introduction to radiotherapy is written for the non-radiotherapist and will be of particular interest to those who work with radiotherapists and who want to know more about the subject.

After reviewing the historical development of the specialty since the discovery of X rays in 1895, it goes on to outline, in a very clear manner, the general principles of radiotherapy and radiation physics. Almost half of the book is devoted to a description of radiotherapy equipment and how it is used. The author has not attempted to describe the treatment of tumours at individual sites but has succeeded in giving a balanced overall picture of treatment planning with both external beam therapy and radium. This section is profusely illustrated with first-class diagrams and photographs of radiotherapy equipment in use.

The book touches on the care of patients before, during and after radiotherapy and includes short chapters on radiobiology, radiation protection and the organization of radiotherapy departments. It finishes with a useful glossary of terms and a list of further reading.

The only criticism of this book is that in parts it is over-simplified. This may make it more acceptable to nurses but definitions of benign and malignant tumours and radical and palliative treatment are probably unnecessary. Nevertheless, this will be a worthwhile book to have in any medical library.

THELMA D. BATES.

1977, *British Journal of Radiology*, *50*, 573–575 AUGUST 1977

The tolerance to re-irradiation of heavily irradiated human skin

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ABSTRACT

The clinical course of a group of 15 female patients treated with X-ray therapy for radiation-induced hypopharyngeal tumours is reviewed. Neither acute nor late skin reactions exceeded those expected in similar radical treatments of patients not previously irradiated. One patient appeared to have been cured by the treatment and four achieved two years' palliation. It is suggested that the tolerance of skin to re-irradiation following a long latent period may approach normal.

The treatment of cancer arising in previously irradiated tissue presents a difficult problem in clinical management. In some situations there is no satisfactory alternative to further irradiation. Re-treatment is practised in many centres and yet there are no accepted parameters of normal tissue tolerance in this situation. Policy at the Christie Hospital has been that in the curative management of tumours of limited sensitivity doses are given up to tolerance levels, and repetition of treatment of the same volume is considered highly inadvisable. Re-treatment is regularly practised following previous low dosage treatments where the tissues had not been irradiated to a full tolerance dose (Paterson, 1963). The experimental results of Hendry *et al.* (1977), demonstrating only about a 10% reduction in X ray tolerance dose six months after a previous irradiation to a full tolerance level, prompted this review of the clinical course of a group of radiation-induced hypopharyngeal and oesophageal tumours, in whom a radiation treatment policy has evolved over a number of years.

TREATMENT GROUP

Fifteen female patients (Table I) have been treated between 1960 and 1976 for proven squamous cell carcinoma of the post-cricoid region, pyriform fossa or upper oesophagus. All patients had a history of fractionated X-ray therapy, often over a number of months, for "thyrotoxicosis" or "goitre" 15 to 50 years before their present illness. The quality of radiation and skin dosages given are not known, but radiation stigmata, ranging from severe (Fig. 1) to mild, were present on the lower anterior and lateral neck skin in the majority of patients. Two patients had previously had surgical treatment for squamous cell carcinoma arising in the irradiated skin. Three patients were on thyroxine for myxoedema but no patients had overt thyroid disease at the time of the second treatment.

TABLE I

DETAILS OF PATIENTS BEFORE THE SECOND COURSE OF TREATMENT

Patient no.	Age (years)	Years from previous XRT	Previous diagnosis	Site of tumour	Stigmata
1	66	35	Goitre	Pyriform fossa	None
2	76	25	Thyrotoxicosis	Post-cricoid	Minimal
3	49	15	Thyrotoxicosis	Post-cricoid	Leathery, telangiectatic
4	61	30	Thyrotoxicosis and heart failure	Post-cricoid	Telangiectasia and pigmentation
5	72	44	Thyrotoxicosis and heart failure	Post-cricoid	Marked
6	74	50	Thyroid	Post-cricoid	Marked***
7	57	35	Thyroid	Post-cricoid	"Leathery"
8	53	30	Thyrotoxicosis	Post cricoid	Mild
9	68	Many	Thyroid	Post-cricoid	Mild
10	63	30	Thyrotoxicosis	Pyriform fossa	None
11	83	30	Thyrotoxicosis	Pyriform fossa	Marked
12	69	42	Thyrotoxicosis	Post-cricoid	Marked
13	58	40	Thyrotoxicosis	Pryiform fossa	Marked
14	69	40	Thyrotoxicosis	Cervical oesophagus	Marked***
15	67	38	Thyrotoxicosis	Post-cricoid	Marked

***Previous surgery for squamous cell carcinoma arising in irradiated skin.

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*We record with regret that Dr. Stewart died at the end of March.

TABLE II

DETAILS OF SECOND COURSE OF RADIATION

Patient no.	Quality	Technique	Overall time (days)	Number of fractions	Tumour dose (rad)	Field size (cm)	"Skin dose"† (rad)
1	250 KV	parallel pair	11	8	3400	10 × 8	3750
2	4 MV	single field	20	15	4500*	7 × 4.5	4250
3	4 MV	single field	5	4	2500	9 × 4.5	2380
4	4 MV	wedge pair	21	16	4000*	7 × 4	2150
5	4 MV	parallel pair	21	16	5000	8 × 4	4250
6	8 MV	single field	20	15	5000	12 × 6	4250
7	4 MV	parallel pair	21	16	4000*	7 × 5	3400
8	4 MV	parallel pair	21	16	5000	8 × 5	4250
9	4 MV	parallel pair	21	16	5250	8 × 5	4460
10	4 MV	parallel pair	21	16	5000	10 × 5	5000
11	4 MV	wedge pair	21	16	5000	5 × 4	2700
12	8 MV	single field	11	8	3000	12 × 6	2700
13	4 MV	3 field	21	16	5250	7 × 5	3300
14	4 MV	parallel pair	21	16	4000*	8 × 4	3400
15	4 MV	3 field	21	16	5250	9 × 5	2750

*Tumour dose supplemented by intra-oesophageal ^{60}Co bougie. Skin dose approximately 50–100 R in two treatments.
†See text.

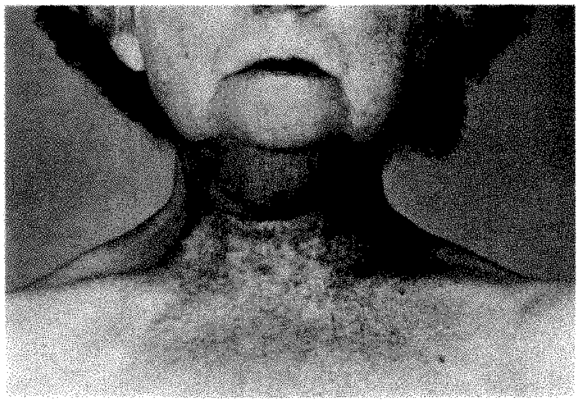

FIG. 1

Patient 11, Skin of lower neck before treatment, showing marked radiation stigmata.

RADIOTHERAPY TECHNIQUE

A variety of techniques were employed in treating these patients, resulting in a wide range of skin doses. This is complicated further by the inhomogeneity of the radiation stigmata, different field sizes, their positioning in relation to the previously irradiated skin, and a fundamental lack of knowledge of what is the critical depth for skin tolerance dosage. In an attempt to present this in a useful form, the "skin dose" is expressed as the minimum dose at 0.5 cm depth over at least 50% of the area of re-treated skin (Table II). In the treatment planning of these patients, attempts were made to avoid the skin showing the most stigmata.

RESULTS

Radiation reaction

No patient had an early skin reaction which exceeded pigmentation or dry desquamation. The clinical course of the reaction in these patients did not differ from that of patients who had no previous history of radiation exposure. The majority of patients received a full radical course of X-ray therapy. During subsequent follow-up, no patient had ulceration or necrosis of irradiated skin and all patients who died did so of recurrent or metastatic cancer, or the pneumonic complications associated with stricture formation. In one patient the neck tissues were "fibrosed and thickened" four years after treatment. Although the long-term follow-up did not exceed three to four years, we are confident that long-term radiation damage did not complicate the clinical course.

Clinical results

As a group, these patients did poorly (Table III). There is only one long-term survivor and only five patients lived two years after treatment. Many had problems with stricture formation at the primary site and succumbed to bronchopneumonia. Four of these were benign strictures and five arose from recurrence of the malignancy. Only two patients died of metastatic disease. The efficacy of irradiation in controlling the primary disease is difficult to assess from the available data, but primary malignancy arising *de novo* at these sites often follows a similar course to that seen in this group of patients.

TABLE III

Follow-up and fate of patients

Patient no.	Follow-up	Fate
1	6 weeks	Died—Pneumonia
2	1¾ years	Died—Pneumonia and stricture
3	1 year	Died—Cerebral metastases
4	9 months	Died—Recurrent local tumour
5	3¼ years	Died—Recurrent post-cricoid
6	10 months	Died—Recurrent tumour
7	2 years	Died—Stricture and carcinomatosis
8	3 years	Died—Post-operative bouginage of stricture
9	3 months	Died—Pneumonia
10	4½ years	Alive and free of disease
11	10 months	Died—Recurrent carcinoma
12	3½ years	Died—Pneumonia and stricture
13	1 year	Died—Recurrent local tumour
14	6 months	Alive and well
15	12 months	Alive and well

Discussion

Ionizing radiation as a carcinogenic factor in hypopharyngeal tumours has been recognized since the 1930s and was extensively reviewed by Goolden (1957). His series of 32 tumours included 12 from this hospital but treatment was not discussed at that time. Garrett (1959), in presenting further cases, mentions the short-term successful use of X-irradiation in some of his patients but the questions of tolerance and dosage were not raised.

The results of the follow-up study of this group of patients with such a wide range of doses to previously heavily irradiated skin suggest that there is considerable tolerance to re-irradiation in such tissue, and there is nothing from the results to suggest that this tolerance does not approach normal. There is, unfortunately, no way that the available data can be extended to define the parameters of tolerance to make this observation of general applicability. It is hoped that other centres will publish their clinical experience in this field so allowing more general understanding of tolerance to re-irradiation both of skin and of other normal tissues. The clinical significance of the results of the experiments of Hendry *et al.*, using the rat tail necrosis model, are supported by the response of this group of patients and suggest that the general principles of tolerance of skin to re-irradiation may be defined more quickly and clearly using this model. Certainly the problem of new or recurrent cancer developing in irradiated tissues is not going to diminish in the forseeable future.

The long-term control of the new malignancy in one patient and the satisfactory palliation achieved in approximately half of the patients encourage us to believe that a second course of X-ray therapy represents a reasonable form of treatment for malignant disease arising in this situation. Successful long-term control of a similar patient has been reported previously (Gowing, 1961). The more accurate dosimetry of such treatments available now may eventually allow the clinical tolerance limits for re-irradiation of human skin to be defined more accurately.

It must be stressed that these observations relate only to skin tolerance and not to the tolerance to re-irradiation of any other tissue. This is felt to be particularly important in relation to tissues like the central nervous system or kidneys where the complications associated with exceeding tolerance are potentially lethal. Clinical observations and laboratory experiments will be needed to identify any recovery of tolerance in these tissues. The observations also related to non tumour-bearing normal skin and shed no light on any influence of a tumour on the recovery of tolerance in a tissue or of the efficacy of re-treating a previously radically irradiated primary tumour.

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The response of the rat tail to hyperthermia

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Abstract

When the cartilage of the tail of a baby rat is exposed to temperatures between 41°C and 46°C either necrosis or a small degree of stunting in growth may occur. Isoeffect curves relating time and temperature for both these endpoints for normal and clamped tissue were found to be parallel, a doubling of heating time or an increase in temperature of 1°C having the same effect in all cases. Clamping sensitizes the tails by a factor of about three in heating time, equivalent to a temperature difference of 1.5°C. Arrhenius plots show an inactivation energy of 140 kcal/mole. This is similar to that found by other workers using different endpoints, and supports the suggestion that protein denaturation is a critical target for direct heat damage.

The use of hyperthermia in the treatment of cancer has recently become the subject of increasing clinical and laboratory investigation. This is because there may be a differential effect between tumour and normal tissue, a hope which is derived from a variety of observations (Robinson *et al.*, 1974; Thrall *et al.*, 1975; Overgaard, 1977). One of these observations, which has been shown many times, is that hypoxic cells *in vitro* are as sensitive or even more sensitive to heat than well-oxygenated cells (Gerweck *et al.*, 1974; Schulman and Hall, 1974). Hypoxic tumour cells may therefore be more sensitive to heat than well-oxygenated normal tissue, the reverse of the situation with X rays.

Few observations of the response of tissues *in situ* to hyperthermia have been made since Moritz and Henriques (1947) using pig skin produced results showing that the time required to produce a specific effect was reduced by a factor of two for each degree centigrade rise in temperature (between 44°C and 51°C), a result later confirmed by Crile (1963) using the feet of mice. Suit (1975) observed that the time of heating required to produce a given skin reaction on the feet of mice heated by water to 43.5°C was reduced to two-thirds when the limb was made hypoxic by clamping. He also observed a dramatic increase in the response of a tumour to heat when its blood supply was stopped with a clamp.

The relationship between heating time and temperature to produce a given level of damage has been investigated for cells *in vitro* (*e.g.* Westra and Dewey, 1971), from which an activation energy of about 140 kcal/mole has been derived. This is consistent with the values obtained for denaturation of some proteins (*e.g.* enzymes). It has not previously been known whether the same value would be obtained for tissue heated in anoxic conditions.

We have used the response of the tails of baby rats to increased temperatures for an investigation, *in vivo*, of the oxygen effect and the relationship between heating time and temperature. The system was chosen because of the ease of heating, rendering the tail hypoxic and measuring the response.

The response of the tail was found to depend in both a qualitative and a quantitative way on the degree of heating. At low levels of hyperthermia (42°C for 100 minutes or 45°C for ten minutes) there were no obvious changes in the tail due to heating alone. However, these levels of hyperthermia were shown to enhance the effects of X-irradiation in producing the type of damage characteristic of X rays in this system, *i.e.* stunting of growth in the treated vertebrae (Dixon, 1967; Myers and Field, 1977). More severe heat treatments, without X-irradiation, produced a different type of response, *i.e.* necrosis, which was measured by loss of a portion of the tail. Such a response can only be produced by very large doses of X rays and even then does not develop as quickly as when caused by heating. Heat alone does cause some stunting of the tail vertebrae, but very little compared with that which may be caused by ionizing radiations.

The response of the tail to heat alone is discussed in this paper. Both the endpoints of necrosis and stunting are considered.

Methods and Materials

Seven-day-old CFHB rats of both sexes were anaesthetized by intraperitoneal injection of 0.07 mg/ml sodium amylobarbitone. Hypoxia was obtained by slipping a rubber cuff onto the base of the tail, up to the level of vertebra 3 (Dixon, 1967). This was done 20 minutes before heating.

Rats were suspended in Perspex jigs over a constant-temperature water bath so that the tails could be immersed in the water to the level of vertebra number 10, a position previously shown to be 0.6 of the length of the tail from the distal end (Dixon, 1967). The water temperature was maintained by a Grant contact thermometer to within ±0.05°C. The stated times of immersion of the tails were correct to within ±10 seconds. The internal temperature of the tail was measured using thermocouples inserted into 25 gauge hypodermic needles, and a check was made that the thermocouples were not in direct contact with the water. For both clamped and unclamped tails, the temperature of the immersed portion was found to rise and stay within 0.1°C of the water bath temperature after five seconds of immersion. The temperature of the unheated portion above the water surface rose slowly but was never greater than 37°C when the water temperature was 44°C. A range of temperatures from 41°C to 46°C was investigated and the heating time was varied for each temperature. Heating times ranged from two minutes at the highest temperatures up to 190 minutes at the lowest temperatures. An average of five heating times was used at each temperature, with nine rats at each point.

After heating, the rats were allowed to recover from anaesthesia in a warm box before being returned to their mothers. After six weeks they were weaned and sexed and after 12 weeks, when growth was complete, the tails were radiographed using a Hewlett Packard "Faxitron" diagnostic X-ray machine at 30 kV and Kodak "Industrex D" paper.

Radiographs were examined for two types of damage:

1. *Necrosis*. After severe heat treatments, such as 46°C for 30 minutes, tails had necrosed by four days after heating and only the ten untreated vertebrae remained out of the normal total of 28. After more moderate treatments necrosis occurred less rapidly and fewer vertebrae were lost. An arbitrary endpoint for necrosis was defined as tails which had lost all vertebrae distal to No. 17 by 12 weeks after treatment.
2. *Stunting*. Some vertebrae remaining after heating were found to be stunted in their growth, and this could be measured on the radiographs using a travelling microscope. Further details of this technique are given in an accompanying paper (Myers and Field, 1977). The stunting of growth after heating is probably due to the killing of stem cells in the epiphyseal plates of the diaphyses, as has been observed after X irradiation (Wright and Howard-Flanders, 1956; Dixon, 1967).

RESULTS

Figure 1 (A and B) gives the percentage of rats having lost their tail vertebrae distal to No. 17 by 12 weeks after heating. These data are given as a function of temperature and heating time both for unclamped and clamped tails. It is seen that at all temperatures, once a threshold level has been reached, the effect of increasing the treatment time is rather dramatic; on average an increase of only about 20% in heating time is required to increase the probability of necrosis from 0 to 100%. As the temperature is increased, the time of heating required to produce necrosis is reduced. From Fig. 1 (A and B) it is clear that the clamped tails are more sensitive than the unclamped.

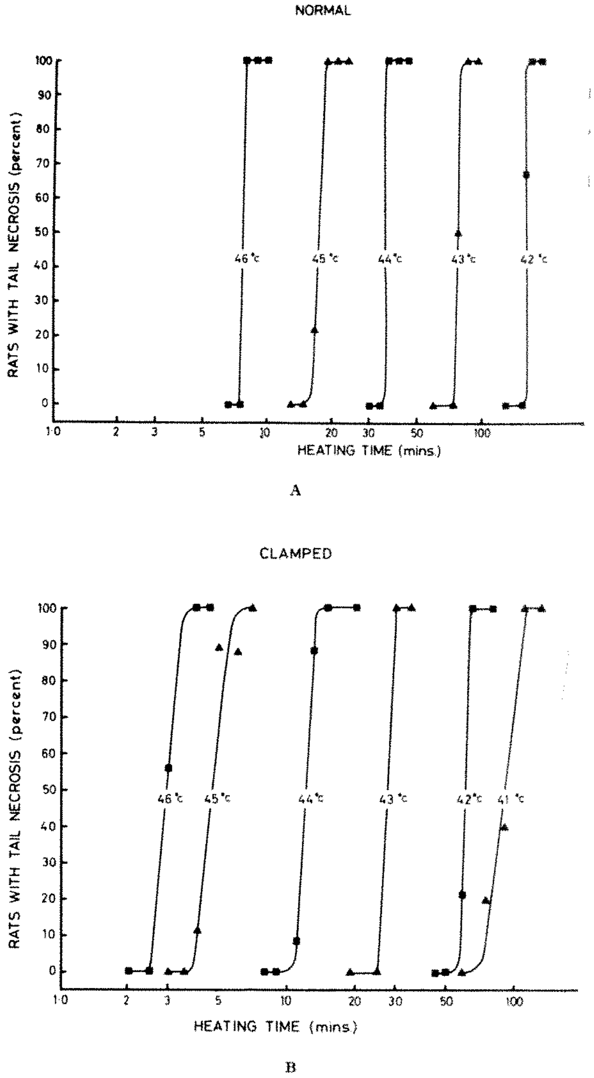

FIG. 1

(A) The effect of heat alone in causing necrosis in the baby rat tail. The percentage necrosis in normal, unclamped tails is shown as a function of heating time for various temperatures.

(B) The effect of heat alone in causing necrosis in the baby rat tail. The percentage necrosis in tails clamped 20 minutes before and during heating is shown as a function of heating time for various temperatures.

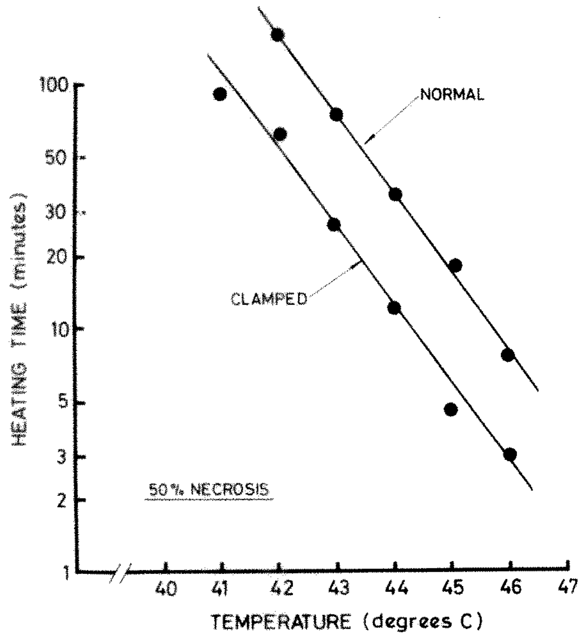

Fig. 2.

The relationship between heating time and temperature to produce necrosis in 50% of the animals treated in either normal or clamped conditions.

The results of Fig. 1 (A and B) have been analysed by estimating the average time at each temperature to produce necrosis in 50% of the rat tails (Fig. 2). It is seen that for each 1°C change in temperature, the time of heating is altered by a factor of approximately two to produce the same level of damage. Since the curves are parallel this relationship is the same for both normal and clamped tails. However, at all temperatures the clamped tails required only one-third the heating time of the unclamped tails to produce 50% necrosis. This is equivalent to a temperature change of 1.5°C.

The results for stunting were less satisfactory than for the endpoint of necrosis. This was because necrosis occurred at a low level of stunting (about 10–15%). Figure 3 (A and B) show the degree of stunting as a function of heating time and temperature (cf. Fig. 1 (A and B) for necrosis). The level of 5% stunting was used to construct isoeffect curves of heating time against temperature (Fig. 4). The features are similar to those described for necrosis (Fig. 2).

Discussion

It is clear from Figs. 2 and 4 that, for both necrosis and stunting of growth in the baby rat tail, the sensitivity to heating is much greater when the tissue has

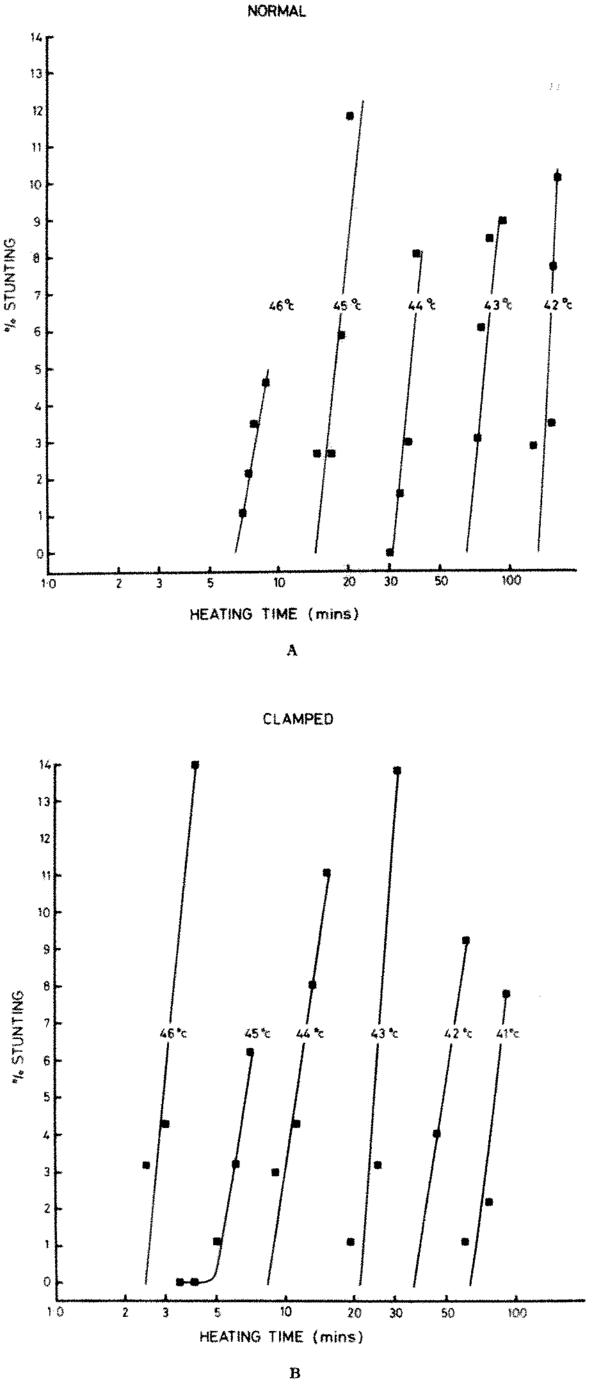

Fig. 3.

(A) The effect of heat alone in causing stunting in growth of the vertebrae of the baby rat tail. The percent stunting in normal, unclamped tails is shown as a function of heating time for various temperatures.

(B) The effect of heat alone in causing stunting in growth of the vertebrae of the baby rat tail. The percent stunting in tails clamped 20 minutes before and during heating is shown as a function of heating time for various temperatures.

been clamped. This result *in vivo* is in general agreement with the results of experiments on cells *in vitro* (Gerweck *et al.*, 1974; Schulman and Hall, 1974; Hahn, 1974). Nevertheless it is not clear whether the effect is actually due to hypoxia, a reduction in pH, a nutritional deficiency of the cells or some other effect of clamping. Certainly cells at low pH are particularly sensitive (Freeman *et al.*, 1976; Overgaard, 1976; Overgaard and Bichel, 1977) and clamping of the tail might cause reduction in pH by means of a build up of lactic acid. Hahn (1974) has shown that thermal sensitivity increases greatly when cells are treated in a salt solution lacking nutrients. Both effects may influence the response of tumours in which hypoxic cells are probably at an abnormal pH and may also be deprived of nutrients (Dewey *et al.*, 1976). It is seen in Figs. 2 and 4 that the slopes of the curves for clamped and unclamped tails are similar, despite a wide range of times of heating and of clamping of tails. This implies that whatever the effect is, it is fully saturated by 25 minutes (20 minutes clamping time plus the shortest heating of about five minutes).

The slopes of all the curves in Figs. 2 and 4 are equivalent to a decrease of a factor of two in heating time for an increase in temperature of 1°C. A similar result has been derived for necrosis of other normal tissues, namely of pig skin (Moritz and Henriques, 1947), and mouse foot and regression of a sarcoma by Suit and Schwayder (1974) from the results of Crile (1963). The calculation of the activation energy from data of this type using the Arrhenius equation was originally made by Henriques (1947). The value he obtained was 150 kcal/mole over the temperature range 44°C to 70°C. He argued that denaturation of numerous proteins occurs with this range of activation energy and suggested that perhaps enzyme denaturation was a primary mode of heat damage. Using cultured mammalian cells, Westra and Dewey

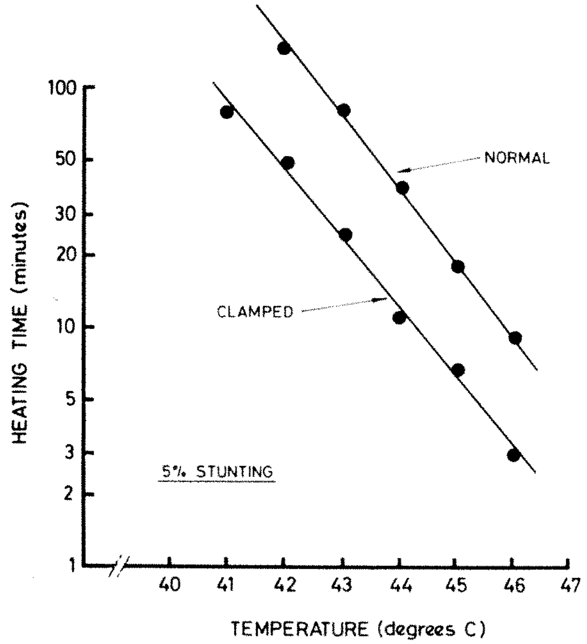

Fig. 4.

The relationship between heating time and temperature to produce 5% stunting in the tails of animals treated in either normal or clamped conditions.

TABLE I

Values of activation energy from the literature compared with the present determinations

Type of cell on tissue	Authors	Temperature range, °C	Activation energy, kcal/mole
Cells *in vitro*			
CHO	Loshek (1977)	43–48	152
CHO	Westra and Dewey (1971)	43.5–46.5	141
CHO	Dewey *et al.* (1976)	43–46	148
CH	Johnson and Pavelec (1972)	41–45	184
CH Lung	Robinson and Wizenberg (1974)	40–42	76
CH Lung	Robinson and Wizenberg (1974)	42–44	161
Pig kidney	Harris (1967)	44–48	121
Tissues *in vivo*			
Pig skin	Moritz and Henriques (1947)	44–70	150
Mouse feet	Crile (1963)	44–49	130
Sarcoma 180	Crile (1963)	41–47	130
Rat skin	Okumura and Reinhold (1977)	42–46	135
Rat tail cartilage in normal conditions	Present results	42–46	144
Rat tail cartilage in clamped conditions	Present results	42–46	144
Rat tail cartilage in clamped conditions	Present results	41–42	?74

(1971) reached a similar conclusion and suggested that perhaps the specific proteins involved were those in the mitotic spindle, quoting activation energies in the range 110–200 kcal/mole (Johnson *et al.*, 1954). These values of activation energy are substantially higher than those for heat induced damage to DNA, *i.e.* 28 kcal/mole for depurination, 25 kcal/mole for strand scission and 34 kcal/mole for loss of transforming ability in viral DNA.

The present results on the rat tail, analysed similarly by means of the Arrhenius equation, give values for the activation energy of 144 kcal/mole for normal and clamped tails. However, a single data point from clamped tails led to a value of 74 kcal/mole between 41°C and 42°C. The results for rat tail are compared with other values of activation energy derived from the literature in Table I. The majority are seen to fall in the range 120–180 kcal/mole for temperatures above 42°C, consistent with protein denaturation as the mechanism of direct heat damage.

CONCLUSIONS

1. Heating can cause a small degree of stunting in growth of the baby rat's tail, but heat exposure greater than that required to produce about 10% stunting will result in necrosis. This is in contrast with the effect of X rays which can cause up to 90% stunting without resultant necrosis.
2. Isoeffect curves relating heating time and temperature for necrosis or stunting, in normal conditions or with the blood supply occluded with a clamp, are all parallel and separated so that a doubling of heating time or an increase in temperature of 1°C have the same effect. This is a similar relationship to that found by other workers and yields an activation energy of about 140 kcal/mole in the range 42°C to 46°C, in good agreement with other values obtained *in vitro* and *in vivo*.
3. Clamping sensitizes the tails to heat by a factor of about three in time of heating, corresponding to a temperature change of about 1.5°C.

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The response of the rat tail to combined heat and X rays

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ABSTRACT

Moderate heat doses which, alone, cause no measurable response in the cartilage of the tail of the baby rat, may potentiate the effects of X-irradiation. The magnitude of the enhancement (the Thermal Enhancement Ratio, or TER) depends upon the heat dose in a similar way to that observed in other normal tissues. The thermal enhancement in the rat tail was also dependent on the dose of X rays, increasing with increasing dose. Potentiation was always greater when heat was applied before irradiation although the difference in TER between heating immediately before or after irradiation was less than 10%. Potentiation of X ray damage decreased steadily to zero as the heat and X-ray treatments were separated by increasing intervals of time. The loss of potentiation was more complete and more rapid when X rays were given before heating, but was also dependent on both the degree of heating and the dose of X rays.

The potential of heat therapy in the treatment of cancer has been known for over 100 years (Busch, 1866) and its use in conjunction with ionizing radiation has been studied for over 60 years (Muller, 1910), but until recently little experimental work had been done to determine the response of tissues to this combination of modalities. If hyperthermia is to be successfully used in the treatment of neoplastic disease the therapist requires a knowledge of the response of both the neoplasm and any normal tissues which are included in the treatment field. For heat combined with X rays there are several parameters which need to be investigated. These include the relationships between time of heating, temperature, dose of radiation and the time interval between heat and irradiation. The aim of the present study was to establish some of these relationships for combinations of heat and X rays as manifested in the response of one normal tissue.

It is now becoming clear that the response of tissues to heat is both quantitatively and qualitatively dependent on the degree of heating. Large heat doses (*e.g.* over 43°C for 90 minutes) cause direct cell killing and a measurable degree of tissue damage. This damage may occur earlier than that caused by X-irradiation and may also be of a different nature (Field *et al.*, 1976). Smaller heat doses (*e.g.* less than 42°C for 1 hour) produce no obvious effect on tissue, but when applied in combination with ionizing radiation the heating potentiates the radiation damage.

This latter phenomenon was investigated on a normal tissue using the response of the tail of the baby rat, following the techniques of Wright and Howard-Flanders (1956) and Dixon (1967). Dixon showed that X-ray damage to the growing cartilage in the tail vertebrae of week-old rats causes a measurable stunting of growth of the vertebrae. The stunting is due to cell killing of the epiphyseal stem cells of the diaphyses. When moderate heat treatments (insufficient to cause any obvious damage per se) are applied to the tail, the response to X-irradiation is greater than but qualitatively similar to that due to X rays alone. In contrast, large heat doses cause tissue necrosis not seen after radiation and this occurs more rapidly than thermally potentiated radiation damage (Morris *et al.*, 1977).

In the present study of the combined effects of increased temperatures and X irradiation, heating by hot water has been used so that any effects found should be due only to the temperature changes induced.

MATERIALS AND METHODS

Seven-day-old CFHB rats of both sexes were treated whilst anaesthetized with 0.07 mg/g body weight of sodium amylobarbitone (Amytal) given intraperitoneally. For heating, the tails were immersed in hot water to the position of tail vertebra no. 10. Details of the technique are given in Morris *et al.* (1977).

Irradiation was given with 250 kV X rays, HVL 1.2 mm Cu at a dose rate of 1.86 Gy/min. The baby rats cooled rapidly after their tails were removed from the water bath, and to prevent them from suffering hypothermia the irradiation jig was placed on a plate heated to about 37°C. With X rays, as with heat, only the portion of the tail distal to vertebra no. 10 was treated. The delay between heating and irradiation was three to four minutes.

After treatment the animals were allowed to recover in a warm box before being returned to their mothers. Most treatment groups were of six animals of mixed sexes. The rats were weaned at six weeks. At 13 weeks, when bone growth was complete, the tails were radiographed on a diagnostic X-ray set and the lengths of vertebrae measured to within 0.01 mm using a travelling microscope over an illuminated viewing screen. Six vertebrae in each

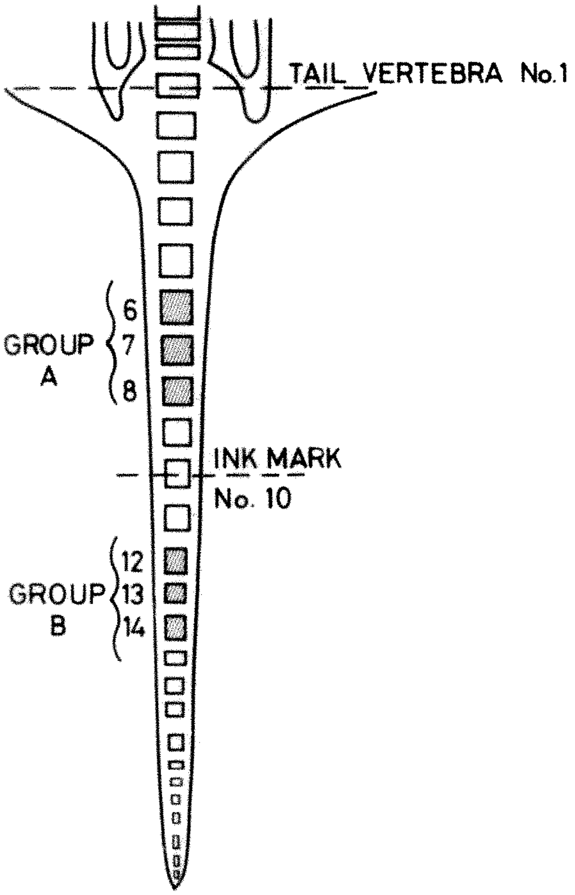


Fig. 1.
Diagram of the tail of a week-old rat.

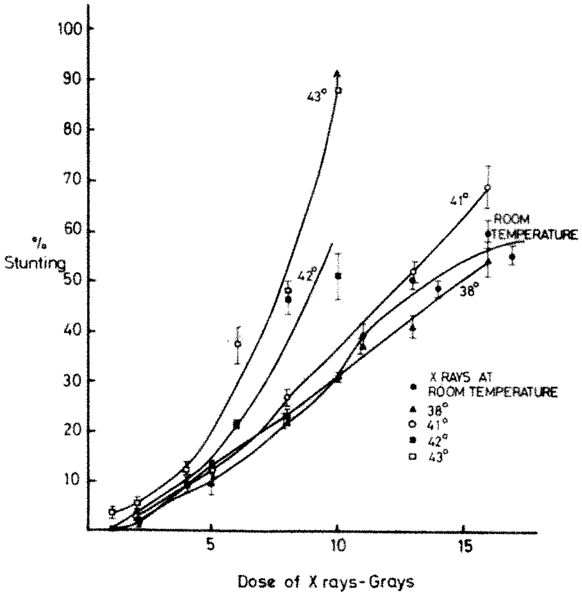


Fig. 2.
Dose-effect curves for stunting induced by X rays given immediately after heating for one hour at one of four temperatures, or alone at room temperature. Points show the mean ± the standard error.

tail were measured, numbers 6, 7 and 8 in the proximal untreated portion, designated group A, and numbers 12, 13 and 14 in the distal treated region, group B (see Fig. 1).

$$\text{Let } \frac{\text{Mean length of group B diaphyses}}{\text{Mean length of group A diaphyses}}$$

$= R$ for untreated rats

$= r$ for treated rats

$$\text{Then stunting} = 1 - \frac{r}{R}$$

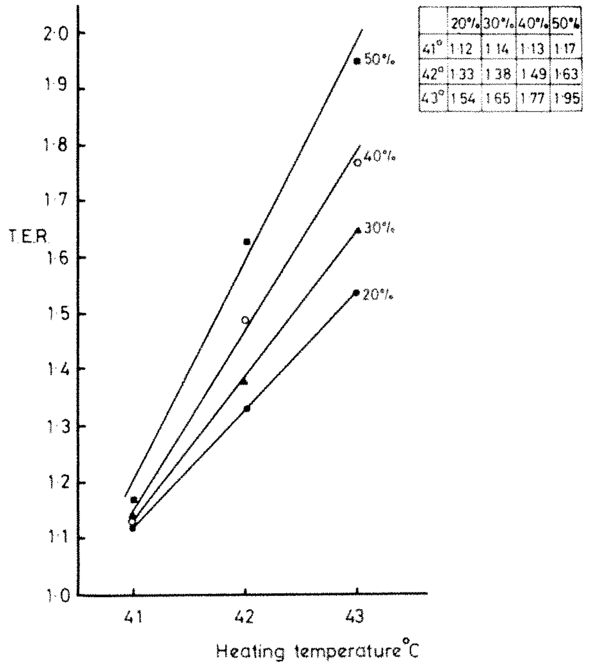
Results

From examination of 59 control animals the value of R was found to be 0.93 ± 0.003. There was no significant difference between males and females or between batches of baby rats.

Two types of experiment were performed. In the first, the enhancement of the effects of irradiation by heating for one hour at various temperatures was determined. In the second the effects of separating the two treatments were measured. There were no qualitative differences noted between the response of the tail to X rays or to the combination of X rays with hyperthermia at any of the temperatures and heating times used.

Figure 2 shows the dose-effect curves obtained by heating the tails at 38°, 41°, 42° or 43°C for one hour before X-irradiation, and for X-irradiation alone. The degree of potentiation of X-ray damage by heat was expressed as a Thermal Enhancement Ratio (TER) defined as Dose of X rays alone/Dose of X rays combined with heat, required to produce a given level of stunting. Values for the TER at various levels of stunting are given in Fig. 3. There was no enhancement of X-ray damage by previous heating to 38°C, but at higher temperatures the TER increased, being about 1.1 at 41°C for one hour and about 1.8 at 43°C for one hour. The TER was also dependent on the dose of X rays, increasing with the X-ray dose and hence with the level of injury.

In the second set of experiments we attempted to assess the temporal relationships between heating and irradiation. Heat was applied 8, 6, 4, 2 hours or immediately before X rays and vice versa. The results are summarized in Fig. 4. Doses of X rays of



	20%	30%	40%	50%
41°	1·12	1·14	1·13	1·17
42°	1·33	1·38	1·49	1·63
43°	1·54	1·65	1·77	1·95

FIG. 3.

Thermal enhancement ratios plotted as a function of heating temperature for four levels of stunting. The inset tabulates the TER's plotted in the figure.

5 Gy or 10 Gy were used with heating for one hour at 43°C, but with 42°C for one hour the X-ray dose was 8 Gy. In each case heat alone caused little or no stunting. The levels of stunting caused by the X-irradiation alone are also shown in Fig. 4.

Some trends are clear. Heat applied immediately before X rays was always more effective than the reverse sequence although the difference was small. As the time interval between heat and irradiation increased there was, on the whole, a reduction in effectiveness. For heat given first, the decay in effect was somewhat slower and smaller in extent than for X rays given first, so that by eight hours after heating there was still considerable potentiation of X-ray damage. For X rays given first the potentiation was lost by four hours.

Times between heating and irradiation of one hour or less were separately investigated for 10 Gy and 43°C for one hour. The results of this experiment are shown in Fig. 5 in which it is seen that the decay in potentiation was most rapid during the first 15 minutes after the initial treatment, whether this was heat or X rays.

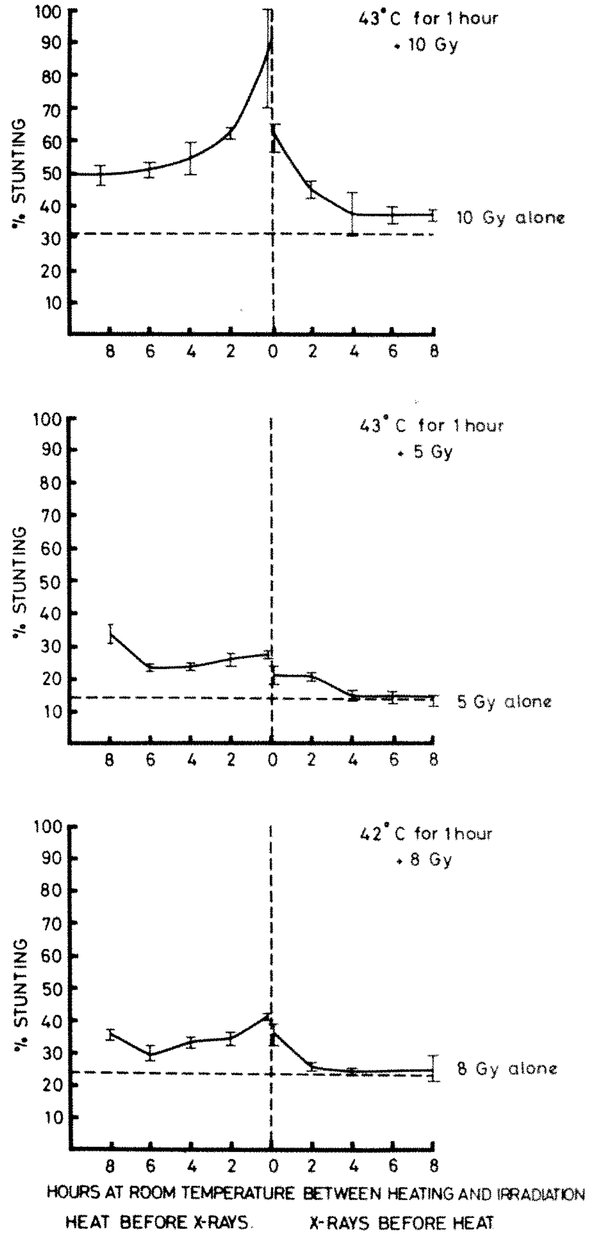


FIG. 4.

The effect of separating the heat and X-ray treatments by varying periods of time. The horizontal dashed line in each case shows the effect of the X-ray treatment given alone. Heat alone in each case caused no measurable damage. Points show the mean ± the standard error.

DISCUSSION

It is known that the response to irradiation of tissues *in situ* is often not the same as that of cells grown in culture. For example, the capacity of cells to undergo repair of sublethal damage is normally much greater for undisturbed tissue. For this reason we questioned whether the response of tissues *in vivo* to combinations of X rays and hyperthermia might be different from the response of cells *in vitro*. We therefore used one normal tissue, the growing cartilage of the baby rat tail, to investigate some aspects of the response of intact tissues to combined heat and X rays, which may be important in the therapeutic applications of this type of treatment.

The experimental system used, stunting of growth of the baby rat tail, has yielded reproducible results for potentiation of the effects of X rays, the response being qualitatively similar to that observed after X rays alone. This potentiating effect of heat on X rays has been measured under various conditions.

Necrosis does not occur as a result of X-ray damage, or heat-potentiated X-ray damage, at the dose levels used. Where very high levels of stunting are obtained, as with 43°C for one hour immediately before 10 Gy of X rays, very little growth of the diaphyses occurs and the bones tend to fuse, making measurement and a precise estimate of the degree of stunting impossible. This is in contrast to the effects of greater amounts of heat given alone (Morris *et al.*, 1977).

The combination of heat and irradiation is known to be more effective than irradiation alone. Whether heating immediately before or after irradiation is the more effective has been the subject of several investigations. No difference was found using *in vivo* systems by Hahn *et al.* (1974), Crile (1963), Robinson *et al.* (1973), Overgaard and Overgaard (1972), Overgaard and Suit (1976) or Stewart and Denekamp (1977). Robinson and Wizenberg (1974) and Kal *et al.*, (1975) used CHL and rat rhabdomyosarcoma cells respectively to show that a greater effect was achieved if heat was applied before X rays, while Ben-Hur *et al.* (1974) using CHf cells obtained the opposite result. Thrall *et al.* (1975) showed that for mouse skin heating first was the more effective, while a C3H mammary carcinoma was more susceptible when irradiation was given first. For both normal and malignant tissues, therefore, only Thrall *et al.*, (1975) working with a mouse tumour have found that X rays given first are more effective than the reverse. With cells *in vitro* no pattern is emerging, but recently Sapareto *et al.* (1976), using CHO cells irradiated at different times during the heating period, showed that the effect was greatest when irradiation was performed early in the heating period.

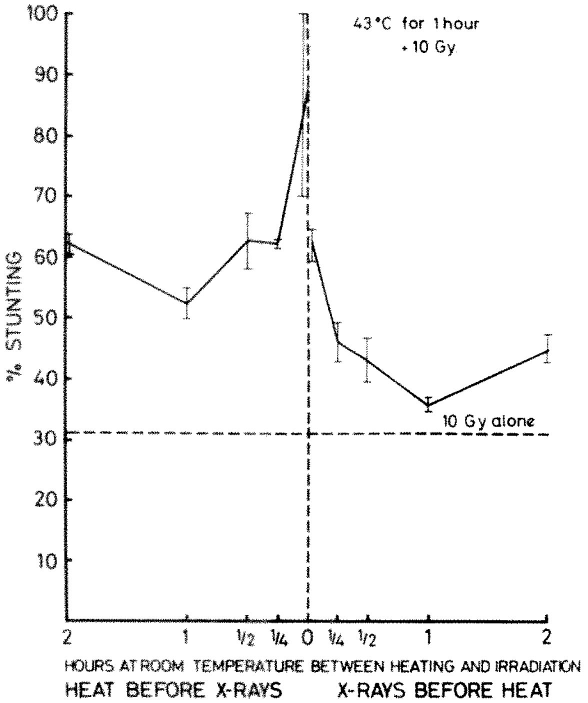


Fig. 5.

The effect of separating 43°C for one hour and 10 Gy of X rays by short periods of time. When heat was given immediately before X rays, damage was too great to be assigned a value. Points show the mean ± the standard error.

In our experiments, we have found heat applied immediately before X rays to be more effective than the converse in every case (Fig. 4). The difference was small, however, amounting to less than 10% in terms of the thermal enhancement ratio. Clearly, if differences in response could be established between normal tissues and tumours they might be exploited to establish an optimum combined treatment régime, but it appears that a greater understanding of the basic mechanisms of both heat and irradiation damage is necessary to make this possible.

From Figs. 2 and 3 it is seen that the effect of heating for one hour becomes noticeable above 40°C, beyond which there is an increasing effect with increasing temperature. The results shown in Fig. 3 are for heating first, the more effective sequence in this system. In Fig. 6 comparison is made with results from other workers on skin and intestine, where heating was also for one hour applied either concurrently with, immediately before, or immediately after irradiation. It is seen that there is only a small variation in the responses of the various tissues and that the response of normal tissues to X rays is greatly potentiated by heat. This must be taken into account by any clinician using these methods. Although the shaded band in Fig. 6 indicates thermal enhancement beginning at 37°C, this is only for skin damage; heating cartilage in the baby rat tail has no potentiating effect on X-ray damage until the temperature exceeds 40°C.

Figure 3 shows that the TER is dependent on the level of damage chosen for its assessment. It has been suggested from work *in vitro* that hyperthermia inhibits repair of sublethal X-ray damage (Ben-Hur *et al.*, 1974). In terms of survival curves this means a reduced shoulder for irradiation at higher temperatures, so that the TER would be greater at lower doses, *i.e.* in the shoulder region. This situation is analogous to the difference in response of cells and tissues to low and high LET radiations. A result which is consistent with this hypothesis has recently been published (Hahn *et al.*, 1976) although the finding is not universal. For example, using cells *in vitro* Loshek (1976) observed an *increased* capacity for accumulation of sublethal damage at raised temperatures. The cartilage system used in the present work exhibits a large capacity for accumulation and repair of sublethal damage after X rays (Dixon, 1969), and the suggestion from our results is that the capacity for repair of sub-lethal injury is slightly increased after hyperthermia, consistent with the finding of Loshek (1976).

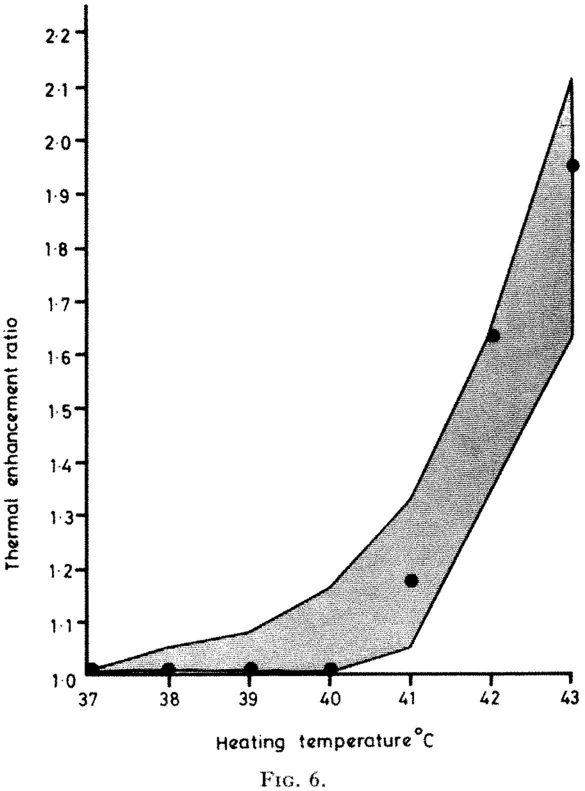


FIG. 6.

The spread of thermal enhancement ratios derived from the results of five studies of normal tissue. The data were obtained from experiments on mouse intestine and mouse ear skin (Field *et al.*, 1976), mouse foot skin (Stewart and Denekamp, 1977; Robinson and Wizenberg 1974) and rat cartilage (in the present work). In the latter case, the TER's were taken from the 50% stunting level (see Fig. 3) and these data are shown as ●. The shaded area represents the standard deviations of the TER's derived from these five sets of data.

In practical radiotherapy it may be convenient to separate the heating and irradiation. The response of tumours might be different from that of normal tissues in this respect and the choice of suitable timing might lead to a therapeutic advantage. Two heat exposures and three irradiation doses have been used to investigate the temporal relationships between heat and X rays. The pattern of response was similar in all cases. When heat was given first the decay in potentiation was less and some effect remained at a separation of eight hours. There was even a tendency for the potentiation to increase between six and eight hours, implying some effect of cell synchrony by the heating. For X rays given first the potentiation decayed to zero by four hours. This pattern is consistent with that observed by other workers using tissue endpoints, *e.g.* Stewart and Denekamp (1977) and Law *et al.* (1977) on skin. Similar results have also been obtained for cells *in vitro* (Kal et al., 1975; Henle and Leeper, 1976).

The mechanism of thermal potentiation of X-ray damage needs to be understood if full use is to be made of this method of treatment. It has recently been found that the reduction in effect when heat is given before irradiation is remarkably similar to the reduction in activation of lysosomal enzymes with time after heating (Hume and Field, 1977), a result which suggests a role of the lysosome in combined heat and X-ray damage.

CONCLUSIONS

1. The response of the rat tail to heat depends qualitatively as well as quantitatively on heat dose. Moderate heat doses cause no measurable effect per se but greatly potentiate damage by X rays.
2. Thermal Enhancement Ratios obtained in rat cartilage heated for one hour are similar to values obtained with other normal tissues.
3. The Thermal Enhancement Ratio is to some extent dependent on the dose of X rays used, increasing with increasing dose.
4. Heat applied immediately before X rays is always more effective than the reverse sequence, but the difference in the TER between the two treatments is less than 10%.
5. Loss of potentiation of X-ray damage by heat is more rapid and complete when X rays are given first.

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A radioprotective effect of vitamin C observed in Chinese hamster ovary cells

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ABSTRACT

Vitamin C at high concentrations was found to inhibit the growth of CHO clone A cells in culture. It had a radioprotective effect, giving a maximum increase in cell survival of a factor of seven under the experimental conditions used. The protective effect was mainly but not exclusively attributable to an increase in the D_0, the maximum increase observed being the order of 1.4.

The interaction of radiation and drugs in producing cellular damage, both *in vitro* and *in vivo*, has been studied extensively in recent years (Okada, 1970; Kaplan, 1970; Elkind and Whitmore, 1967). The motivation for these investigations includes a desire to be able to manipulate or control radiosensitivity. It is also hoped that interpretation of specific interactions will provide insight into the mechanisms of development and repair of radiation damage (Orr *et al.*, 1975; Dertinger and Jung, 1969; Malone and Foster, 1972; Siemann *et al.*, 1975). The groups of agents studied have generally been cytotoxic drugs, metabolic inhibitors, oxygen or substances mimicking the dose modifying action of oxygen, while other known radioprotectors and sensitizers have also been considered (Bleehen *et al.*, 1974; Sheldon *et al.*, 1976; Adams, 1970, 1974; Pihl and Sanner, 1970).

In contrast, the influence of ordinary metabolites or metabolic intermediaries on radiation response has been subject to very little investigation. However, a few of the substances studied, such as cyclic-AMP and oxygen in its role as a metabolite, suggest that this may be a fruitful field worthy of further exploration (Foster *et al.*, 1970; Lehnert, 1975; Siemann *et al.*, 1975). It is likely that an effect of some such agents on radiation response may be exploited both in radiotherapy and radiological protection, simply because their concentrations may be more easily and safely manipulated than those of cytotoxic drugs. They may also be better tolerated by patients than existing radiosensitizers.

In this paper the influence of vitamin C on the radiation response of Chinese hamster ovary cells is examined. A radioprotective effect is observed which may be relevant to the management of radiotherapy patients in view of the known difference in the vitamin concentration between tumours and normal tissues (Moriarty *et al.*, 1977). It may also have consequences in radiation protection both for victims of acute accidents and for those likely to be given large diagnostic exposures (Ala-Ketola *et al.*, 1974).

MATERIALS AND METHODS

Chinese hamster ovary (clone A) cells, originally obtained from Dr. T. R. Munro, were used throughout. The culture techniques have been described in detail elsewhere and are briefly reviewed here (Malone *et al.*, 1974). Cells were propagated as monolayer cultures in disposable plastic flasks (Falcon), in Ham's F-10 medium buffered with 25 mM Hepes and supplemented with 15% calf serum. Antibiotics were not used in this medium. The cells were detached from the flasks, during routine subculture or cloning experiments, by rinsing the monolayer in a 0.1% trypsin solution in Ca and Mg free balanced salts solution (BSS). This was followed by 4 min incubation at 37°C in a fresh aliquot of the same trypsin solution. Gentle pipetting then resulted in a monodispersed cell suspension. Trypsin action was halted by addition of an equal volume of growth medium. The cell suspension was counted in a Coulter Model D counter using a 100 micron orifice.

During experiments, appropriate numbers of cells from stock cultures in log growth phase were inoculated into 25 cm^2 disposable tissue-culture flasks (Falcon or Sterilin), in a final volume of 5 ml of growth medium. After overnight incubation, vitamin C (Sigma) dissolved in BSS was added to yield appropriate final concentrations. The medium containing vitamin C was changed daily for the duration of exposure, which was generally three days. Controls were treated identically, but vitamin C was omitted. At the end of the period of exposure to the vitamin the cells were trypsinized and counted as described above. Alternatively they were irradiated, still in the vitamin C medium. Two to three hours after irradiation they were trypsinized, counted and plated onto

25 cm^2 disposable flasks in 5 ml of medium, at concentrations expected to yield 100 viable clones per flask. These flasks were incubated for six to seven days at 37°C, and then fixed and stained in 1:15 Carbol-Fuchsin. All macroscopic colonies were scored as viable (Elkind and Whitmore, 1967; Monk *et al.*, 1973). In cases of doubt the colony was examined microscopically and the 50 cell criterion applied (Elkind and Whitmore, 1967). Clones from selected radiation points and controls were examined microscopically to determine if any gross changes in morphology had taken place.

Irradiation was carried out with 250 kV X rays, filtered with 1 mm Cu, obtained from a Stabilipan unit. The exposure rate, measured with a Siemens dose meter, gave an absorbed dose rate of 190 rad/min. Error bars (standard errors) are displayed where they are larger than the point on the graph.

Vitamin C was assayed using a modification of the Densen and Bowers (1961) technique. After trypsinization the cells were centifuged for 10 min at 3000 r.p.m. in a glass tube. The supernatant was discarded and 2 ml of 5% trichloroacetic acid added. The residue was ground and the tube allowed to stand for 20 min after which it was centrifuged for 5 min at 3000 r.p.m. From the supernatant 1.5 ml was removed and added to 0.5 ml of 2:4 dinitrophenylhydrazine. After incubation at 37°C for four hours the mixture was cooled in an ice bath and 2.5 ml of 65% H_2SO_4 was added. The resulting mixture was allowed to come to room temperature and read at 520 nm in a spectrophotometer (Beckman). A standard containing 6 μg of vitamin C was similarly prepared, and the reading from a blank containing the above reagents except vitamin C was subtracted from all other readings. The concentration was expressed in μg/10^8 cells.

RESULTS

Figure 1 shows the normal growth pattern of CHO cells, together with the influence of vitamin C on the yield of cells after four days incubation. The CHO cells divided with a doubling time of about 13.5 h. Low concentrations of vitamin C did not appear to interfere significantly with this. However, high concentrations of vitamin C dramatically reduced the cell yield particularly at 100–300 μg/ml. The yield of cells was of the order of 2–3% of that in the control. This was evident even from visual inspection of the cultures, as the medium with high concentrations of the vitamin contained debris from dead cells.

In Table I the influence of three days preincubation in various concentrations of vitamin C on

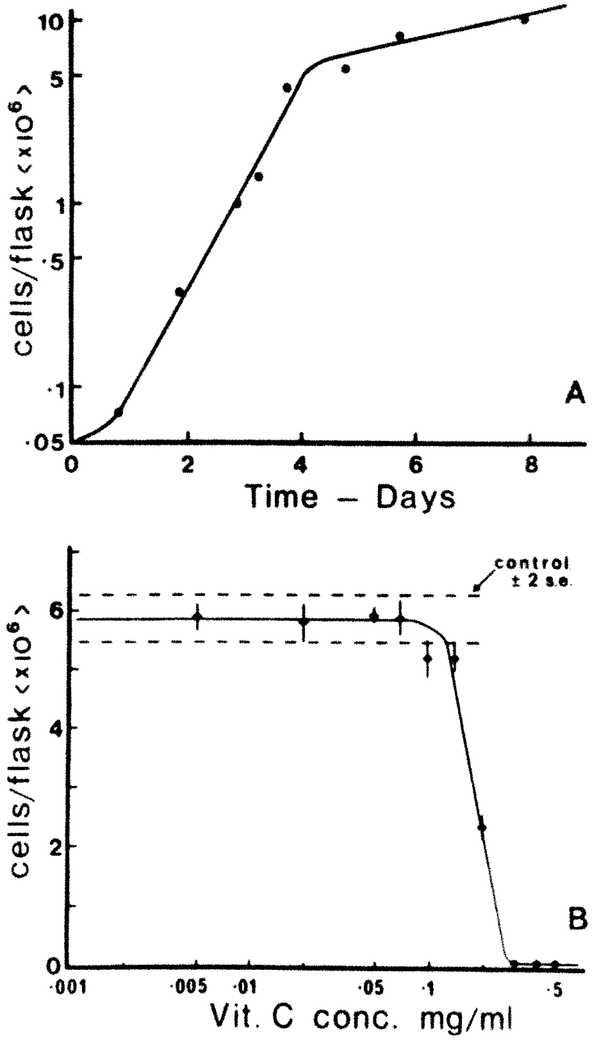

FIG. 1.

(A) Growth curve for CHO cells. (B) Effect of various concentrations of vitamin C on yield of CHO cells after three days incubation.

TABLE I

CLONING EFFICIENCY OF CHO CELLS AFTER EXPOSURE TO VARIOUS CONCENTRATIONS OF VITAMIN C. CONTROLS (0 mg/ml) NORMALIZED TO 100%

Vitamin C conc. mg/ml	Cloning efficiency ±2 S.E.
0.0	100 ±12.0
0.02	95.9± 4.4
0.10	104.4± 4.4
0.30	108.2± 4.7

the cloning ability of the residual cells is presented. There was little effect on the cloning ability in the concentration range used.

In Fig. 2 the level of vitamin C per 10^8 cells is plotted as a function of the level in the medium. The medium levels are plotted on a logarithmic scale and the cell levels on a linear scale. Clearly the relationship is not one to one, but as the medium levels increase, the cellular levels eventually do also. Since it is not clear which is significant at this stage both are presented.

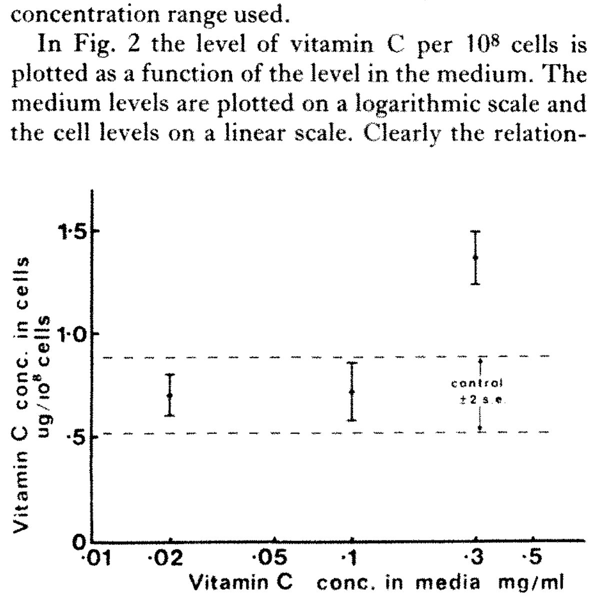

FIG. 2.

Relationship between concentration of vitamin C in media and concentrations of vitamin C in cells.

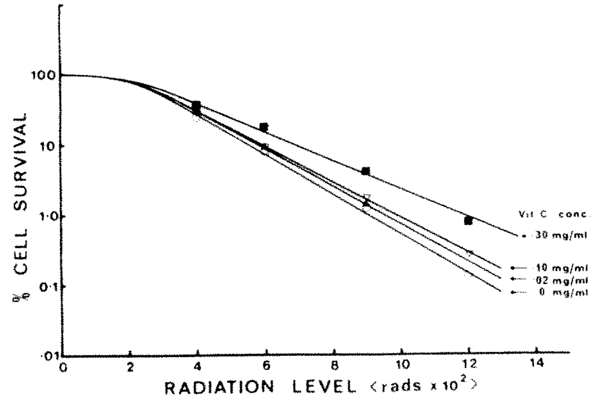

FIG. 3.

Survival curves for CHO cells grown in various concentrations of vitamin C. Cells irradiated during log-growth phase at 37°C.

Figure 3 shows survival curves for CHO cells irradiated with concentrations of vitamin C ranging from 0 to 300 μg/ml in the medium. Clearly the presence of the vitamin had an effect on survival, which increased with its concentration. The extrapolation numbers and D_0 values for the survival curves are listed in Table II, and show that both are influenced. The D_0 increases significantly and the extrapolation number is subject to a small decrease at high vitamin concentrations. The dose modifying factor (ratio of D_0 values) at the highest vitamin C concentration used is about 1.4.

Finally, while quantitative data on this point are not presented, it is worth recording that there was a striking macroscopically evident increase in the size of clones from cells irradiated in the presence of vitamin C. This was confirmed microscopically, which further revealed that clones from these irradiated cells retained the fibroblast morphology even at 1200 rad. This was not the case with controls (Carroll, 1976).

DISCUSSION

The doubling time and growth properties of CHO cells found here are comparable with previously reported values (Malone *et al.*, 1974). The data in Figs. 1 and 2 suggest that concentrations of vitamin C in the medium below 100 μg/100 ml have little or no effect on cell growth. Where the yield of cells is considerably reduced after three days incubation with high levels of vitamin C in the medium, the cloning efficiency of the cells retained on the flask was not significantly reduced. Toxic effects of vitamin C on cell cultures have been previously reported by Schwerdt and Schwerdt (1975). They found that 50 μg/ml produced noticeable effects in log growth phase cultures of W1-38 cells, but that plateau phase cultures could tolerate concentrations up to 350 μg/ml. These concentrations compare well with those

TABLE II

SURVIVAL CURVE PARAMETERS

Vitamin C conc. mg/ml	D_0 rad	Extrapolation no. n	Dose modifying factor (ratio of D_0 values)
0.0	155	3.7	1.00
0.02	160	3.5	1.03
0.10	170	2.9	1.10
0.30	215	2.4	1.39

reported here in relation to toxic and growth inhibiting effects. Other work bearing on a toxic effect of vitamin C includes numerous studies of anti-tumour potential of the vitamin and ascorbate derivatives, which have generally been carried out *in vivo* and demonstrate that these compounds exert an inhibiting effect on tumour growth (Omura *et al.*, 1974; Yamafugi *et al.*, 1971).

The vitamin C concentration in the medium in the above experiments, 20–300 μg/ml, is not far removed from the normal range of values encountered *in vivo*. Plasma levels lie between 3 and 10μg/ml, but can be as high as 40 μg/ml. Tissue levels can be 400 μg/ml and average body concentration, when saturated, is about 50 μg/ml (Documenta Geigy, 1970). Therefore, the concentration ranges for the media in these experiments are comparable with those encountered biologically. The cellular concentrations resulting from these levels in the medium were in the range 0.5–1.5 $\mu g/10^8$ cells. This indicates that the cellular concentration can be considerably lower than concentration in the medium as 10^8 cells correspond to a mass of about 0.1 g. This finding is compatible with *in vivo* results which indicate that plasma levels of vitamin C are frequently not directly related to cellular levels. Furthermore, it is worthy of note that recent findings indicate that different tissues in the body, particularly tumours and normal tissues, contain different levels of vitamin C. For example tumours have been demonstrated to have a vitamin C concentration which is about 2.4 times that of the surrounding tissue (Moriarty *et al.*, 1977; Documenta Geigy, 1970). As the radiation effects observed may be attributable to either the cellular levels or the levels in the medium, both are cited in Fig. 2.

The radioprotective effect of vitamin C illustrated in Fig. 3 is striking, and in a sense paradoxical, as the protective effect is greatest at the most toxic concentration used. The largest dose modifying factor observed, 1.4, resulted in an increase in survival by a factor of 6.5 at a dose level of 1200 rad. While this is not as large as the oxygen effect, it is clearly of some importance in view of the fact that vitamin C levels are open to a considerable degree of variation and manipulation *in vivo* (Documenta Geigy, 1970). The mechanism of the protective effect cannot be suggested by the experiments reported here, but effects due to partial synchronization of the population cannot be excluded as the status of the cells in this regard has not been determined (Sinclair, 1972). However, such effects seem unlikely to be entirely responsible for the radioprotection, since if they were one would not expect the gradual increase in the dose modifying factor with concentration up to 100 μg/ml (Fig. 3; Table II) that occurs while there is relatively little change in cell yield after three days incubation. The possibility that radical scavenging effects play a part must also be considered.

The radioprotective effect here occurs after three days incubation in medium containing vitamin C. Further work is necessary to determine if the full three days incubation is necessary, or if the effect occurs at an earlier stage, or if the presence of the vitamin in the medium after irradiation is necessary. The suggestion of a change in extrapolation number (Fig. 3; Table II) also indicates that other studies on the time course of the events will be necessary to determine whether or not Elkind recovery is influenced (Elkind and Whitmore, 1967).

The literature on the influence of vitamin C on radiation response is not extensive when compared with its status in many other fields (Bacq, 1965). However, a substantial radio-protective effect on the survival of rats subjected to whole body irradiation has been reported (Ala-Ketola *et al.*, 1974). It has also been used in the management of victims of acute radiation accidents, but probably not with the intention of exploiting the type of effect reported in this paper (Bacq and Fischer, 1957). In relation to therapy of human cancers, there appears to be no consensus of the vitamin C levels that should be achieved in the patient. Recommendations range from complete elimination from the diet during radiotherapy (Miller and Sokoloff, 1955), to use of massive doses in terminal cases (Cameron and Campbell, 1974; Cameron and Pauling, 1974). As well as contributing to the overall condition of the patient these régimes may seriously influence the radiation response. In particular the therapeutic ratio, which is a measure of the differential between the radiation response of the tumour and normal tissue, could be subject to variation with vitamin C level. This is because recent work has demonstrated a significantly higher level of the vitamin in tumours (Moriarty *et al.*, 1977) than in the surrounding tissue, which could result in a protective effect for the tumour. Finally, it is conceivable that advantage might be taken of the vitamin C protective effect, by local application, to promote skin sparing.

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Technical note

A safer coupling collar for the Cathetron linkages

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It goes without saying that in the operation of the Cathetron intracavitary unit the drive cable must be firmly attached to the source cable. If this is not achieved then it is possible for a source to be pushed out of the safe and into the treatment catheter without the assurance of it being withdrawn again to the safe position. It is of the utmost importance to guard against this possibility.

The coupling of the two cables is by a simple hook and eye arrangement as shown in Fig. 1. This is an effective link because once it is covered by a tube of diameter slightly larger than the cables the hook is too large to come out of the eye. The tubes carrying the source to the catheter satisfy this condition. When the link has been coupled a split cylindrical collar with a central channel is immediately placed around it to prevent disengagement of the exposed hook and eye (Fig. 2b). A cover is then slid over the collar to keep it closed. However these collars can sometimes be awkward to use due to stiffness and non-parallel movement of the hinges at the top and bottom of the collar. This is made worse by the fact that the radiographer coupling the link has to keep the hook and eye engaged with one hand and close an awkward collar at the same time with the other hand. If both hands are used to manipulate the collar then it is quite easy for the weight of the drive cable and its cover to unhook the link. Furthermore, the collar has to be maintained shut whilst the cover is slid over it.

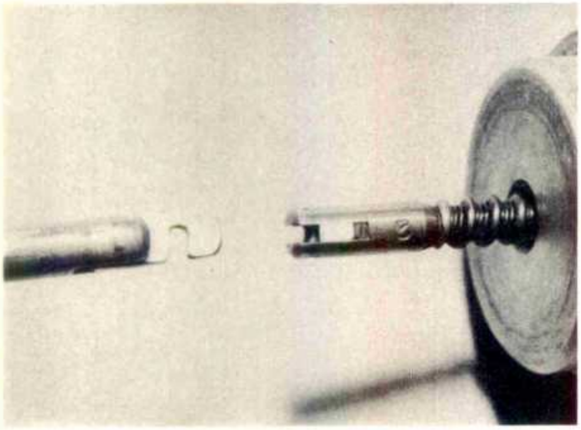

FIG. 1.
The hook and eye linkage.

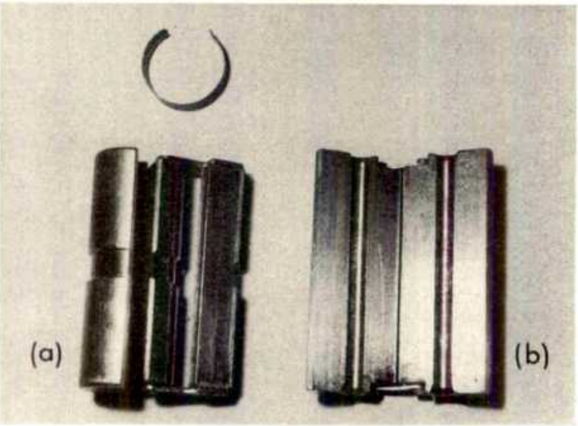

FIG. 2.
(a) New slotted collar with recess for circlip.
(b) Old collar.

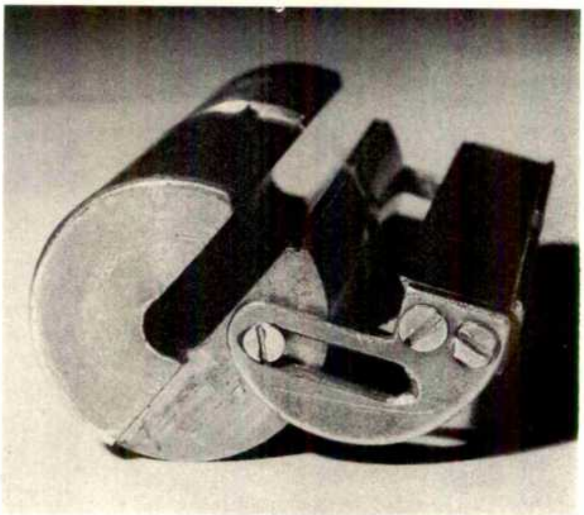

FIG. 3.
Slotted collar—the hinged section.

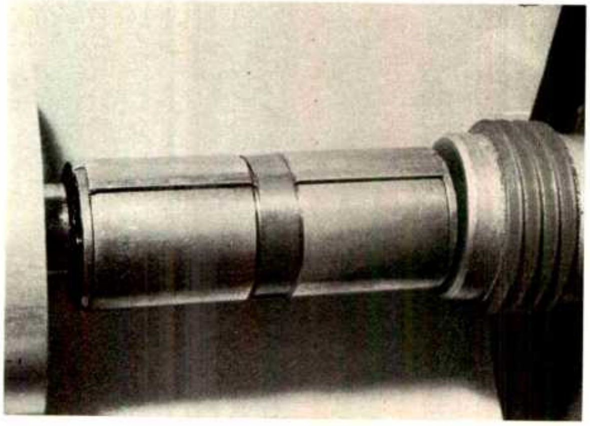

FIG. 4.
New collar in place.

On at least three occasions over ten years of almost daily use a source has been driven out which could not be retrieved due to an unmade link—the latter presumably caused when doing this awkward operation. A similar situation has occurred elsewhere.

We have made new collars which help in several ways. First, as shown in Fig. 3, the coupled cables have a slotted collar slid over them. The direction of the slot opening can be chosen at right angles to the movement of the hook so that once the link is in the slot it cannot come apart.

Secondly (Fig. 3) the mobile hinged section of the collar is rotated and dropped into the slot—an operation we have found to be far easier than that of bringing the two halves of the original collar together.

Thirdly, once the slot has been filled, a recessed circlip which is shown in Fig. 2a can be rotated a few degrees to secure the mobile section of the collar in place. The collar can no longer come apart. This now leaves both hands completely free to rotate the circlip a full 180 deg. and then to test the connection, which is presumed still to be secure, by gently pulling on the cover. If not secured the hooked end will be pulled out of the slot. The completed connection is shown in Fig. 4. Finally, both hands are free to slide the cover over the collar for attachment at the Cathetron safe.

Book review

Medical Images: Formation, Perception and Measurement. Proceedings of the Seventh L. H. Gray Conference held at the University of Leeds, 13–15 April 1976. Edited by George A. Hay, pp. ix + 368, 3 colour plates, 1976 (The Institute of Physics, John Wiley and Sons), £12·50.

This first venture of the L. H. Gray Trustees into diagnostic methods is a reflection of the recent rapid growth of new imaging technology. The first section, occupying about half the book, has chapters on each of the new imaging devices—CT scanning, NMR imaging, ionography, coded aperture work, sophisticated ultrasonic imaging and ultrasonic microscopy, Compton camera, transverse emission tomography, and thermography. Individual contributors have had to confine themselves to explaining basic principles, avoiding gruesome details. The result is a concise and fairly critical summary of the merits of the many new techniques which are now, or soon will be, available to the clinical diagnostician, presented in a form which at least his physicist colleagues should find easily readable. This is followed by a short section dealing with general methods of assessing the performance of the devices with respect to image quality and "noise". While silver halide emulsions do not qualify as new imaging devices this section and much of the discussion of quality and perception in later sections is equally applicable to them.

It is at first disappointing that F. W. Campbell's fascinating lecture on the transmission of spatial information through the human visual system is reported only in summary, supported by an extensive bibliography of the original sources of his data and illustrations. This may, however, be more useful to the serious reader than any necessarily abbreviated version of the lecture, with few illustrations, would have been. Threshold mechanisms in the presence of noise and methods of assessing the performance of observers are also discussed in this section. Section 4 continues the search for quantitative methods of assessing "image quality" and discusses the effect of some image-processing techniques on "quality". The last section considers the value of extracting strictly numerical information from a variety of imaging systems—cineangiograms, ultrasonic signals, T.V. chromosome analysis—you name it!

Can one small book usefully carry all this varied information? It succeeds, as did the conference, surprisingly well. The specialist cultivating one small corner of the field learns what his partner (opponent?) in another corner is up to, without feeling that he is being talked down to. While the typography is good, it seems a pity that the paper quality does not do justice to those illustrations which require a good grey scale: but that is a minor criticism of a very useful book which will retain its value longer than do most conference proceedings.

J. W. BOAG.

1977, *British Journal of Radiology*, *50*, 594–596

Case reports

The "invisible" can top

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(*Received February, 1977*)

ABSTRACT

The hazard of ingestion of a beverage can top in a child is presented. These can tops are of surprisingly low radio density and their presence can be overlooked on a conventional P.A. X ray of the chest. In such cases a lateral radiograph of the chest should be included in the routine investigation of the child.

The ingestion of a foreign body by an infant or young child is a common occurrence in paediatric practice. In most cases uneventful passage through the gastrointestinal tract is the expected outcome (Spitz, 1971; Baraka and Bikhazi, 1975). Impaction occurs most frequently in the upper third of the oesophagus and endoscopic removal is usually accomplished. The diagnosis is made on obtaining a positive history and may be confirmed by radiological demonstration of the foreign object, either by its intrinsic radioopacity or by a contrast study. Occasionally the episode may escape attention, and the child may present at a later date with dysphagia, stridor or recurrent respiratory infections. In such cases demonstration of the ingested object may be accomplished by plain radiography of the chest, by a contrast swallow or endoscopy. Aluminium can tops are of surprisingly low radio-density and may easily be missed on radiological examination (Editorial, *Lancet*, 1976). Delay in diagnosis may result in an impacted can top ulcerating through the wall of the oesophagus into the mediastinum. Erosion of one of the major vessels in the thorax has caused the death of at least one young child (Burrington, 1976).

A case, recently encountered, illustrates the hazards of impaction and the pitfalls in diagnosis.

CASE REPORT

An 18-month-old male toddler was admitted to an outlying hospital on February 10, 1976, in acute respiratory distress, having choked on a piece of sausage. An emergency tracheostomy was performed following which the child recovered. The tracheostomy tube was removed the following day and he was transferred to the Sheffield Children's Hospital for investigation of apparently long-standing dysphagia and regurgitation of food during and after meals.

On admission he was noticed to have moderate respiratory stridor and became acutely distressed when feeding. His intake was restricted entirely to semi-solid food. The only relevant feature of his past medical history was failure to thrive from the age of approximately ten months. His weight on admission was 8160 g, well below the 3rd centile for his age and height (75 cm). A plain P.A. radiograph of the chest was unremarkable (Fig. 1).

A barium swallow performed on February 17 revealed a persistent stricture at the junction between the upper and middle thirds of the oesophagus. It appeared as if this part of the oesophagus was slightly displaced anteriorly and to the left by an extrinsic mass. No hiatus hernia or gastro-oesophageal reflux could be demonstrated (Fig. 2). A duplication cyst was suspected.

An oesophagoscopy performed on February 25 revealed a stricture in the oesophagus 12 cm from the incisor teeth. No mucosal abnormality was noted and the stricture easily dilated to F 23 bougie. Bronchoscopy was normal. A repeat barium swallow and endoscopic examination two weeks later showed no improvement and it was decided to submit him to surgical exploration of the oesophagus.

The oesophagus was approached via a right postero-lateral thoracotomy through the bed of the unresected fifth

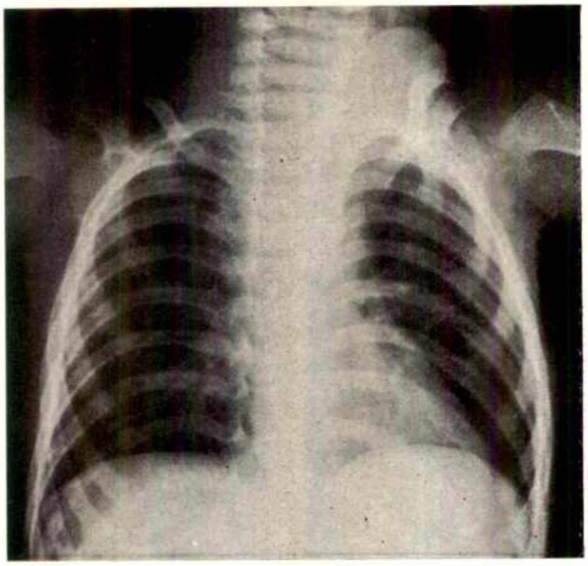

FIG. 1.

P.A. radiograph of the chest showing no evidence of the retained aluminium can tab in the upper oesophagus.

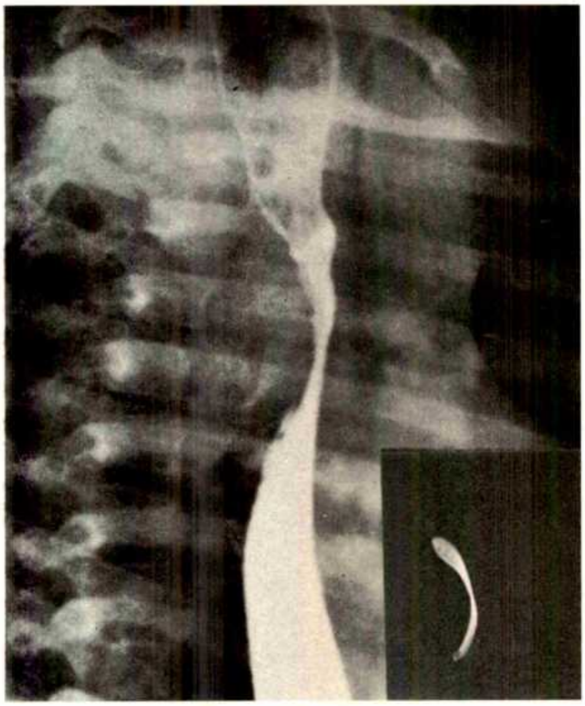

FIG. 2.

Barium swallow showing a persistent stricture at the junction between the upper and middle thirds of the oesophagus and displacement of this part af the oesophagus anteriorly and to the left by an extrinsic mass. Inset shows the X ray appearance of the removed can tab. This can be seen as a faint curved shadow behind the compressed segment of the oesophagus.

rib. A 3 × 4 cm cystic mass was found lateral and posterior to the upper oesophagus just within the thoracic inlet. The mass was densely adherent to the surrounding structures and the oesophagus. It was carefully dissected free from the adjacent tissues and removed leaving a small 0.5 cm defect in the right lateral wall of the oesophagus. Prior to its removal, the mass was inadvertently ruptured revealing the presence of a metal can top within its substance. The defect in the oesophagus was repaired and the chest closed with drainage.

The post-operative course was relatively uneventful. A repeat barium swallow showed some residual distension of the oesophagus above the level of the repair. Barium, however, flowed freely through into the lower oesophagus. In the first two months post-operatively he has gained 2200 g. He remains asymptomatic and is thriving six months post-operatively.

Histological examination of the resected specimen revealed a squamous epithelial lined lumen surrounded by muscularis mucosae and a well-formed muscular layer. Subacute inflammatory reactive changes were present. The features are those of an oesophageal diverticulum into which the can top had impacted.

DISCUSSION

Aluminium pull tops are common items among the detritus of our age. Their shiny appearance and small size make them both attractive and easily ingestible by infants; they are frequently found in areas where infants and children play. The rolled profile and sharp edge, where separation from the ring has taken place, makes the danger of perforation a considerable hazard. Absorption of the X-ray beam by aluminium is low and when such a foreign body overlies bone, as would be the case when a tab lies in the oesophagus and is projected over the spine, the radiograph may fail to show the foreign body. Radiographic recognition is more likely on a lateral film where the density is summated across the width of the tab. Under "ideal" conditions (*i.e.* the aluminium specimen directly on top of the film cassette, and no scattered radiation present), a contrast of about 1.7% per 0.1 mm Al thickness, can be achieved at 65 kVp, so that for an optimally exposed radiograph, thicknesses down to about 0.1 mm Al should be able to be discerned. Under the same conditions thin sheet steel (or "tinplate") produces a contrast of about 20% per 0.1 mm—*i.e.* about ten times greater.

However, under "real" conditions, where the metal sheet is within a body, 10–20 cm from the film, and considerable scattered radiation is present, contrast is reduced to such an extent that small thin pieces of aluminium are completely invisible, and even steel sheet only produces a contrast of about 1.6%/0.1 mm so that the minimum detectable thickness of *steel* is of the order of 0.12 mm.

At present, ring pull cans manufactured mainly by the "Metal Box Company" have walls and base of "tinned" sheet steel of thicknesses 0.16 and 0.28 mm respectively, while the top (with the "tear-out" tab) is of aluminium alloy of thickness 0.35 mm.

It would seem, therefore, that for a "tab" which might be swallowed by children to be visible on a radiograph, the only practicable solution would be for the top of the can to be made of tinned steel (or copper—which would be more easily torn open, but more expensive). Alternatively, consideration might be given to the addition of some distinctive radio-opaque marker to the tab only.

In the case reported a triangular shadow was in fact noted on an oblique film taken during a barium swallow examination, but attempts were made to identify this as a bony structure and its true identity was not recognized.

A recent history of ingestion of a foreign body without subsequent symptoms may not merit X-ray examination; however, persistent difficulty in swallowing and/or respiratory symptoms require a radiological study which should then include a lateral view of the chest as well as the conventional P.A. or A.P. film. A barium swallow may aid in defining the level of spasm or stricture in the oesophagus.

Many beverage cans carry a message asking that litter be avoided. The pull tab may be a hazard to the appearance of the environment, but is infinitely more dangerous as a cause of morbidity and possible mortality among infants and young children.

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Familial pheochromocytoma: a rare case of hydronephrosis and hydroureter in two generations

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(*Received February, 1977*)

Ureteral obstruction from pheochromocytoma is rare (Allen *et al.*, 1971). The unique occurrence of obstruction of the ureter from a functioning extra-adrenal pheochromocytoma, in the same location, in a mother and son 21 years apart is presented.

Case Reports

Case 1

A 13-year-old white female was studied because of impared vision. She gave a history of six months of headaches, irritability, palpitations, and shortness of breath. On examination she was lethargic, had bilateral papilledema, and was severely hypertensive at 220/140 mm Hg.

An intravenous pyelogram demonstrated mild right caliectasis and hydroureter (Figs. 1A, 2A). The distal right ureter tapered abruptly approximately 2 cm above the ureteral orifice.

A 5 cm, encapsulated, firm, yellow tumour embedded in the bladder wall was found at operation. A second tumour, 4 cm in diameter, was discovered in the true pelvis at the right iliac bifurcation. Postsurgical response was excellent, and the patient remains normotensive 21 years later.

Case 2

A ten-year-old boy, son of the above patient, developed frontal headaches following a baseball game. The headaches increased, and he had nausea, projectile vomiting, and a generalized grand mal seizure. The patient was admitted to the University of California Medical Center where his emergency room blood pressure was found to be 165/125 mm Hg., and he had a second grand mal seizure. An intravenous urogram demonstrated right hydronephrosis and hydroureter, but no signs of an adrenal mass (Figs. 1B, 2B). The distal right ureter appeared to be displaced in a craniad direction, and the posterior aspect of the bladder appeared indented from the right (Fig. 2B).

An abdominal aortogram disclosed a vascular blush anterior to the lower right sacral foramina, associated with a lifting and partial obstruction of the right ureter. A right common iliac arteriogram demonstrated neovascularity in the tumour (Fig. 3). No other tumour foci were identified. Computerized tomography confirmed the obstructing mass (Fig. 4).

Biochemical evaluation revealed a striking elevation of urinary and plasma norepinephrine and slight elevation of urinary and plasma epinephrine levels, consistent with an extra-adrenal location of a pheochromocytoma.

At surgery an infiltrating 4 × 2 cm mass was found that extended to the pelvic wall and was densely adherent to the distal right ureter, bladder wall, vas deferens, anterolateral rectum, and sacrum. Wide excision of the mass with segment of encompassed ureter was performed followed by ureteral reimplantation. Careful search of the abdomen for other lesions was negative.

Gross and microscopic examination of the specimen showed a yellow-white, multilobulated pheochromocytoma with multiple foci of vascular and perineural invasion. One lymph node in the area of the neoplasm was almost completely replaced by tumour.

Postoperatively the blood pressure dropped to 90/60 mm Hg. Approximately three months after surgery the patient is well and normotensive.

Discussion

Familial pheochromocytomas have been well described in the past (Carmen and Brashear, 1960; Tisherman *et al.*, 1962). While most familial pheochromocytomas show no definite relation to other diseases, a significant number are associated with some neurocutaneous syndromes, particularly neurofibromatosis (approximately 5% of pheochromocytomas) and von Hippel-Lindau syndrome (Melmon, 1974). In addition, a strong link has been made between medullary carcinoma of the thyroid and pheochromocytoma (Sipple's syndrome) (Nourok, 1964).

Involvement of the lower urinary tract by pheochromocytoma is distinctly uncommon. Of 24 cases of pheochromocytoma involving the bladder

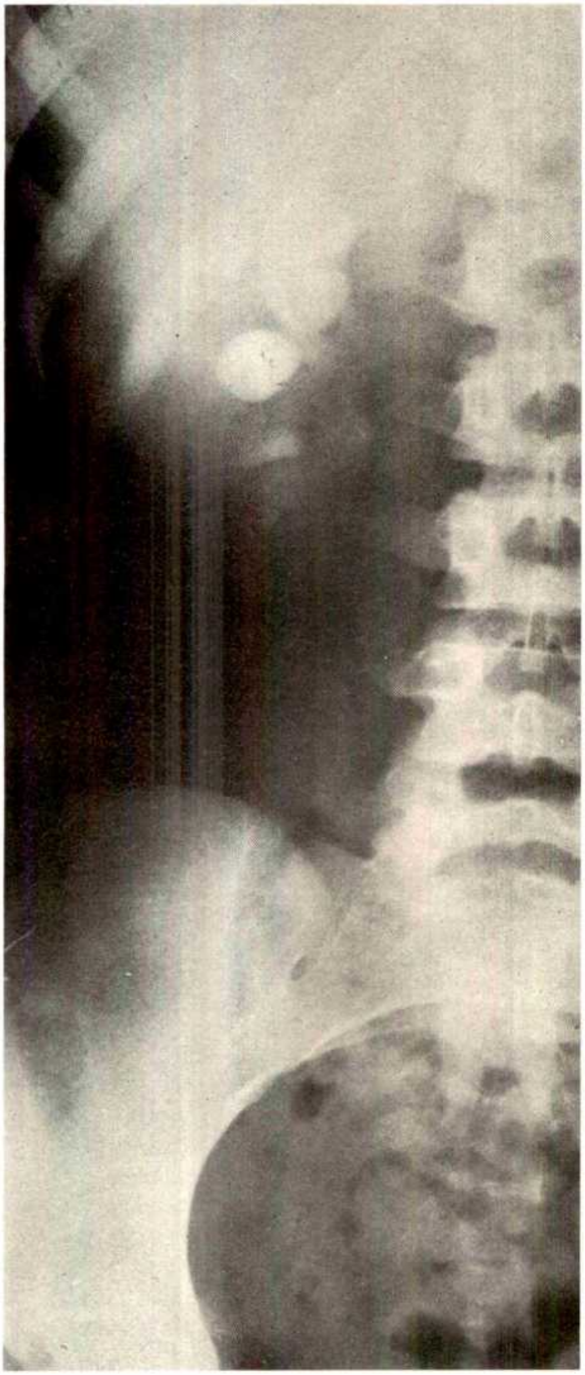

FIG. 1A. *Case 1.*

Intravenous pyelogram of the mother demonstrating right hydronephrosis. Radiograph has been reproduced from a microfilm of 1955 study.

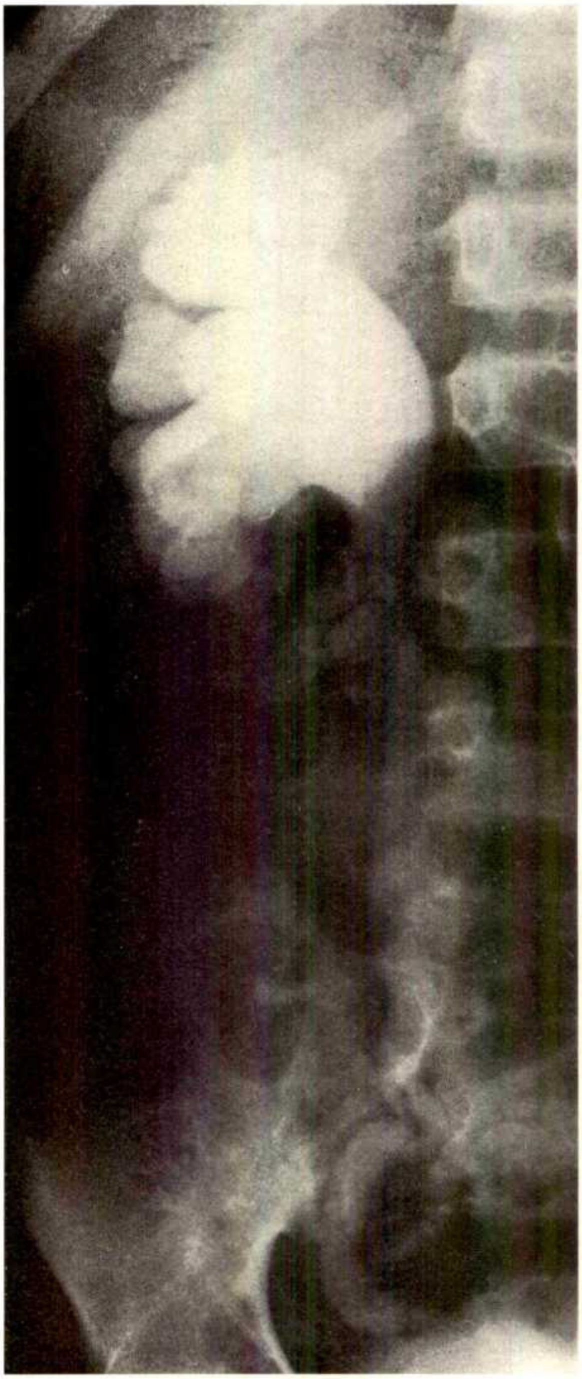

FIG. 1B. *Case 2.*

Delayed pyelogram film of the son showing right hydronephrosis.

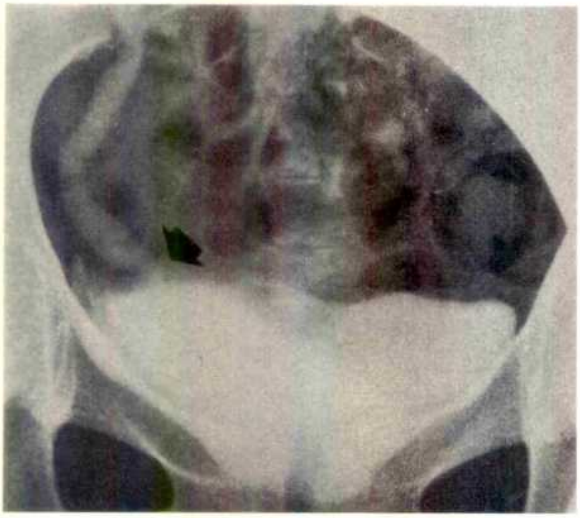

FIG. 2A. *Case 1.*
Intravenous pyelogram of the mother demonstrating right hydroureter, with tapering just craniad to the right ureteral orifice (arrow).

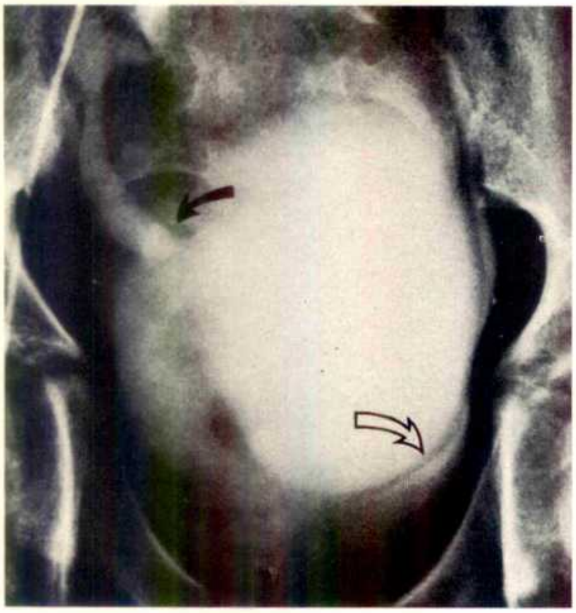

FIG. 2B. *Case 2.*
Postinjection abdominal angiogram of the son demonstrating similar tapering right hydroureter with ureter displaced craniad (closed arrow). Normal position of the left ureter (open arrow).

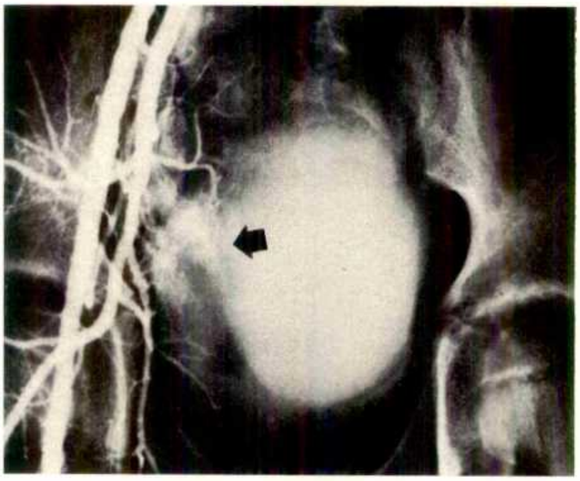

FIG. 3. *Case 2.*
Right common iliac arteriogram. Hypervascular right pelvic mass (arrow), corresponding to the area of right ureteral displacement.

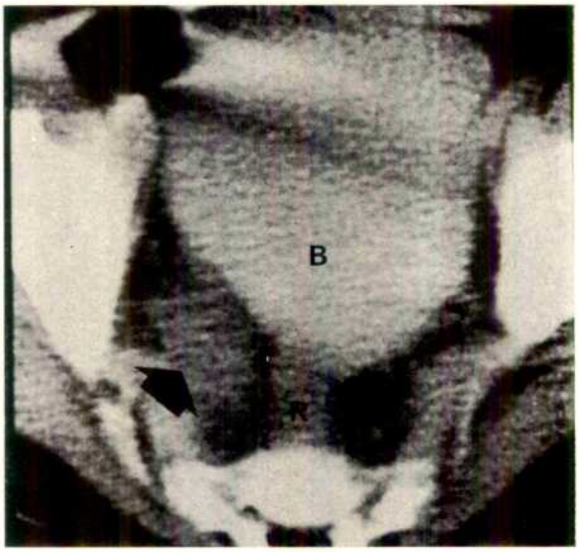

FIG. 4. *Case 2.*
Computerized tomogram at the level of midsacrum showing bladder (B) impressed from right posterolateral aspect by mass (arrow). (R): rectum.

reviewed in 1969 by Albores-Saavedra (Albores-Saavedra *et al.*, 1969) only two involved the ureteral orifices. Involvement of the lower ureter by pheochromocytoma has been reported only rarely (Allen *et al.*, 1971).

Both mother and son in this report presented with the unusual radiographic manifestation of hydronephrosis and hydroureter secondary to pheochromocytomas at the same site. This remarkable similarity in location in this instance of occurrence of familial extra-adrenal pheochromocytoma should alert the clinician, radiologist and surgeon to examine carefully the same locations for extra-adrenal neoplasms.

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Book review

Computed Brain and Orbital Tomography. Technique and Interpretation. By Carlos F. Gonzalez, Charles B. Grossman, and Enrique Palacios, pp. xii+276, 200 figs. (Chichester, John Wiley), £21·76.

This book succeeds in its objective of providing a good introduction to cranial and orbital computed tomography. The first two sections dealing with basic physical principles and sources of error and artefacts assume no previous knowledge, providing a very adequate description in simple language, illustrated by multiple diagrams. The third section, devoted to diagnostic approach, stresses the importance of correlating clinical features with CAT appearances, many of which are not specific for a particular pathology. The normal anatomy is illustrated by brain slices cut in the planes commonly used in computed tomography, mounted beside comparable tomograms.

The following three sections which deal with pathology are presented as a copiously illustrated atlas of generally well selected and clearly reproduced 160 matrix EMI scans. The axis and position of each scan is indicated on a small diagram adjacent to it. The scans are described and discussed in relation to clinical history, other investigations including conventional neuroradiological studies and the established pathology.

The final chapter contains brief mention of "recent advances", including the use of intrathecal Metrizamide, most of which have now been accepted into routine practice in appropriate cases.

The balance of the book is good. In a few conditions, for example meningiomas, colloid cysts and tuberous sclerosis some of the illustrations are similar and could have been reduced without detracting from the book; perhaps illustrations of more artefacts could have been included to advantage, but these are minor points. There is a good index and a selection of key references.

Radiologists experienced in computed tomography who have read the now extensive literature will not find anything new in this book but it is recommended, as a most useful introduction, to those who are commencing study of the sub speciality.

BRIAN KENDALL.

1977, *British Journal of Radiology*, *50*, 600–601

Short communication

Slow repair after X-rays and fast neutrons

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(*Received January*, *1977*)

Two of the most important known phenomena which influence the response of cells and tissues to fractionated doses of ionizing radiation are recovery from sublethal injury and repopulation of surviving cells. The first of these is usually reduced with high LET irradiation, whereas repopulation is thought to be the same after all types of irradiation.

Recently another repair process has been postulated to occur between doses of radiation, but only in tissues for which the normal generation time is long (Field *et al.*, 1976). The authors of this paper analysed the results of irradiation of lungs of mice and noted that as the overall treatment time was increased more radiation was required to achieve an LD_{50}. The effect was called "slow repair" because the half time for the increase was about ten days (in contrast with the half time for recovery from sublethal damage of an hour or two). It was argued that slow repair could not be explained by slow cellular repopulation either by local survivors or from circulating polyfunctional cells because the time course of the increase in LD_{50} would have been different from that observed.

The results of Field *et al.* (1976) were derived from various fractionation schedules and there was a single data point with neutrons which gave a similar value of slow repair to that for X rays. Whether or not slow repair is the same after fast neutrons as after X rays is of such importance that it was felt necessary to repeat and extend the experiment, using two doses of X rays or fast neutrons separated by various time intervals.

The TO mice used in the earlier work were no longer available and female CFLP mice were used instead. Irradiation was given with 250 kV X rays or with fast neutrons from the Medical Research Council cyclotron at Hammersmith Hospital. The thorax alone was irradiated and the mice died from pulmonary damage between 40 and 180 days after treatment, as before.

The two doses of radiation were given at time intervals ranging from one hour up to five weeks, and the results are given graphically in Figs. 1 and 2. The figures show the LD_{50} between 40 and 180 days as a function of the time interval between the two fractions. In Fig. 1 for X rays the LD_{50} is seen to increase to a maximum at about six hours, presumably due to rapid repair of sublethal injury. The sensitivity of the system is variable between six and 24 hours as has frequently been observed with other cells and tissues. Beyond 24 hours there is a steady increase in LD_{50}, as was reported in the earlier work using TO mice, although the rate of increase in LD_{50} beyond 24 hours was rather less than observed in the earlier experiments. The earlier results for two fractions are also shown in Fig. 1 for comparison. The exponent of the *T* factor in the Ellis formula (Ellis, 1969), which is the final slope of the curve in Fig. 1, is calculated to be about 0.03–0.04 for X rays compared with 0.07 derived initially (Field *et al.*, 1976) and 0.06 from Wara *et al.* (1973). Figure 2, for fast neutrons, indicates a significant rapid recovery from sublethal damage in the first hour. The fluctuations are absent and there is no further slow repair up to five weeks, in contrast with the response to X rays. The previous neutron data point is shown for comparison and is clearly aberrant.

We therefore observe slow repair after X rays but not after fast neutrons. This adds weight to the argument that the slow repair process is not simply cellular repopulation, since there is no reason to believe that there are substantial differences in repopulation after different types of irradiation whereas there may be differences in the accumulation and repair of sublethal events as has been shown for the Elkind type of sublethal damage which is repaired rapidly.

The consequences of the observation that slow repair occurs for X rays but not for high LET radiation are far reaching. For slowly proliferating tissues, which are those

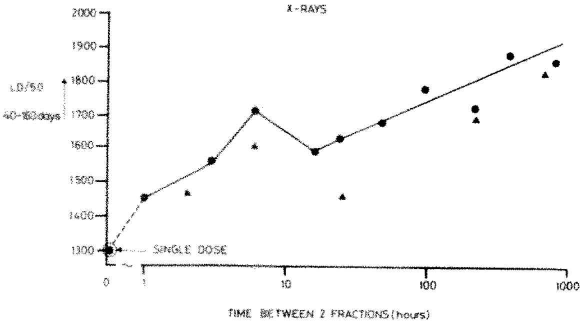

FIG. 1.

The LD_{50} for lung damage in mice after irradiation of the thorax, as a function of the time interval between two fractions of X rays. Time is plotted on a logarithmic scale. ● present results; ▲ results from Field *et al.* (1976).

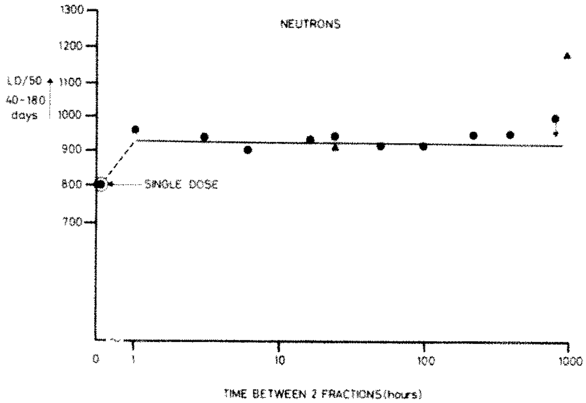

FIG. 2.

The LD_{50} for lung damage in mice after irradiation of the thorax, as a function of the time interval between two fractions of fast neutrons. Time is plotted on a logarithmic scale. ● present results; ▲ results from Field *et al.* (1976).

responsible for late radiation damage, the RBE for late effects would be expected to increase with increasing treatment time. In other words late damage is spared by using a lengthy overall treatment time with X rays but not with neutrons. The result also implies that re-treatment after neutrons would be more hazardous than after X rays, slow repair occurring only after the X rays.

Evidence to support this hypothesis comes from Hendry *et al.*, (1977) using the endpoint of late necrosis in irradiated tails of rats. They found more late necrosis, relative to early skin damage, after pre-treatment with neutrons than after X rays. In addition we have found that the RBE of fast neutrons for acute skin reactions is about 25% greater when the treatment is spread over 26 weeks than when it is given in three weeks (Field, 1977). Even though the skin has a moderately rapid turnover time of about four or five days, the difference in slow repair seems to have some effect.

We believe that more work is necessary on this topic, in particular with other slowly proliferating normal tissues.

ACKNOWLEDGMENTS

We are grateful to Caroline Morris, R. Myers and P. Warren for excellent technical assistance.

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Book review

Radiographic Anatomy of the Chest and Abdomen. By D. Noreen Chesney and Muriel O. Chesney, pp. 278, illus., 1976 (Oxford, Blackwell Scientific Publications Ltd.), £8·50.

This book illustrates structures normally seen in standard projections of the chest and abdomen. Anatomy of the structures is described, accompanied by some line diagrams, but only so far as is needed to elucidate the radiographs.

The first four chapters cover the thorax—postero-anterior, lateral and oblique projections, and contrast studies. Differences due to posture, positioning, build and respiratory phase are included.

The fifth chapter is on the plain abdomen, and the remaining seven on contrast examinations of that area. Appearances due to fat and muscle are shown, as well as those due to calcification.

Barium studies of the gastro-intestinal tract occupy two chapters, and the urinary and biliary systems are also well covered, both by "bread and butter" as well as more complex examinations.

The last chapters are concerned with contrast examinations of liver, spleen and adrenal glands, lymphatic and female reproductive systems.

It is a pity that presentation of some of the radiographs is poor, particularly some in the abdominal sections. One is faced with large areas of grey, in which no detail is visible—many radiographs are not side marked which, as the book is intended for student and junior radiographers, is not ideal. My other criticism is that arrows might have been better for labelling small structures, rather than the large letters which are used.

However, this will be a valuable book for those for whom it is intended. It is well arranged and clearly set out, and will be usefully employed near the film viewing area of an X-ray Department.

Elizabeth C. Salmon.

1977, *British Journal of Radiology*, *50*, 602–603

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

RADIOTHERAPY PILOT TRIALS WITH SENSITIZERS OF HYPOXIC CELLS: METRONIDAZOLE IN SUPRATENTORIAL GLIOBLASTOMAS

Preliminary results of a two-arm randomized pilot study in glioblastoma patients were reported elsewhere last year (Urtasun *et al.*, 1976). These results indicated that the group of patients receiving metronidazole four hours before irradiation of the brain had a significant delay in the time of tumour recurrence. The logical explanation was that in this group of patients the time of tumour regrowth was delayed due to a higher degree of inactivation of the radio-resistant hypoxic cell population (Urtasun *et al.*, 1976).

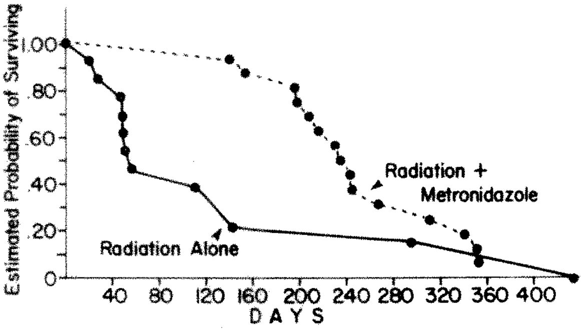

FIG. 1.

Kaplan–Meier survival plots showing the probability of surviving past time *t* for patients with glioblastomas receiving radiation alone and radiation plus metronidazole. The superiority of the metronidazole group survival is significant at the 0.01 level (Wilcoxon–Gehan test statistic).

We would like to report now a follow-up on this study. Out of the 33 patients who were adequately treated there have been four violations of protocol because systemic chemotherapy was initiated at the time of relapse. Consequently, the two groups are now reduced to 13 patients in the control arm receiving radiation only and 16 patients in the group receiving radiation plus metronidazole. All patients are now dead due to recurrence of tumour, except one patient in each group surviving 398 days (control group) and 390 days (metronidazole plus radiation group). The Kaplan–Meier Survival Plot (Kaplan and Meier, 1968) shown in Fig. 1 indicates that the difference between the two groups remains quite striking. The Wilcoxon–Gehan Test Statistic, which at 6.93 with 1 deg of freedom corresponds to a significant level smaller than 10^{-2}, indicates the superiority of the survival in the radiation plus metronidazole group. This confirms, without any change, what was predicted when most of the patients were still surviving (Urtasun *et al.*, 1976).

A new pilot study was initiated in November 1976. In this study the best therapeutic regimen of the previous two groups is compared to the best fractionated conventional

TABLE I

SUPRATENTORIAL GLIOBLASTOMAS

(GRADE IV ASTROCYTOMAS ONLY)

STRATIFIED	*FUNCTIONAL GROUP A*	*RANDOMIZE*	*(1)*	*Rad. Control*	*- 187 rads X 30 - 6 weeks* *Total 5500 rads (NSD - 1650 rets)*
			(2)	*Metronidazole as Radiosensitizer*	*- 430 rads X 9 - 3 weeks* *Total 3870 rads (NSD 1650 rets)* *+ Metronidazole before each fraction*
	FUNCTIONAL GROUP B		*(3)*	*Metronidazole Cytotoxicity?*	*- Same as Rad. Control + metronidazole 3 times/week 4 hours after radiation*
			(4)	*New Agent RO-07-0582*	*- Same as Arm (2) but using 0582 instead of Metronidazole*

END POINT: Survival first day of treatment to time of death
CCNU 80 mg/m^2 q 4 wks. in all patients at time of completion of R$_x$.

RO-07-0582: 1 to 1.5 gm/m^2 *Metronidazole: 6 gm/m^2*

radiotherapy currently used in the Brain Tumour Cooperative Study Groups. The details are given in Table I. The aims of this new pilot clinical trial are: (1) to determine any difference in the survival rate and relapse-free interval with unconventional high dose radiation plus metronidazole at three fractions a week for three weeks as compared with conventional high dose radiation alone with the best available fractionation; (2) to determine whether the action of metronidazole is related in part to its possible chemotherapeutic effect. The drug is administered several hours after radiation treatment; (3) to determine if Ro–07–0582, a superior *in vitro* and *in vivo* sensitizer, could induce an even better delay of tumour regrowth. The proposed dosage of this drug is considerably lower than metronidazole because of its high risk of causing neurotoxicity (Urtasun *et al.*, 1976; Urtasun *et al.*, 1977).

Yours, etc.,
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THE EDITOR—SIR,

A SURVEY OF TISSUE SUBSTITUTES AND PHANTOMS IN 90 EUROPEAN AND NON-EUROPEAN CENTRES

At the Third European Congress of Radiology held in Edinburgh during 1975, a survey of the tissue substitutes and body phantoms in current use was initiated. Following the Congress, a limited mailing of the questionnaire distributed in Edinburgh augmented the number of participating centres and produced data from 90 medical centres in 15 European and non-European countries.

The aims of the survey were three-fold. Firstly, the current usage of "tissue equivalent" systems was to be investigated. Nearly 80 substitute materials have been introduced during the past 70 years (White, 1974) and the acceptance of these systems, outside their centre and country of origin, is not known. Secondly, comments were invited on the usefulness of the existing materials and phantoms, so that any problems with these products could be highlighted. Thirdly, participants were asked to list their future requirements. These comments were intended to act as a guide to future research and development in the field of tissue simulation.

The results of the survey are summarized in Table I. The top row of the table shows the participating countries. Ten centres from seven countries (Belgium, Greece, Finland, Denmark, Spain, Switzerland, Yugoslavia) are classified as "Misc".

It is apparent that body phantoms in five categories are currently being used. The commercial anthropomorphic phantoms designated in the table "Alderson" and "Temex" (Alderson *et al.*, 1962; Stacey *et al.*, 1961) are used respectively by 33 and 15 of the 90 centres. Eighteen centres use phantoms in the form of water-filled plastic shells, some apparently containing real skeletons and artificial lungs. Body phantoms constructed at individual centres, designated "homemade" in the table, are used by 27 centres. The phantoms produced by the Minnesota Mining and Manufacturing (3M) Co., primarily teaching aids, are mentioned by only two centres.

In total, 95 body phantoms, commercial and home-made, are currently available in the 90 centres, an indication of the importance placed on these systems for experimental studies. Nineteen centres commented that they require realistic body phantoms specifically for applications in diagnostic radiology, and 17 centres currently using the commercial Alderson and Temex models commented on the small, Asiatic skeletons used in the systems. Some centres mentioned the high cost of commercial phantoms and the need for greater realism in future models.

Although nearly 80 different substitutes have been published in the past, only 14 tissue substitutes and bolus materials are used fairly extensively, indicating perhaps that many formulations are used solely at their centre or country of origin.

The only bone substitute is aluminium and is used by four of the 90 centres. The most popular muscle substitutes (number of centres in brackets) are water (51), wax (35), Mix D (34) (Jones and Raine, 1949), polystyrene (30), Perspex (25), Temex sheets (24) and Pressdwood (17). Other, less popular substitutes are the wax-based material M3 (Markus, 1956) used by three and nylon used by two centres. Polyethylene, presumably a fat substitute, and the lung substitute, cork, were both mentioned by four centres.

The principal bolus materials are Lincolnshire bolus (Lindsay and Stern, 1953), wax, rice and water. The popularity of Lincolnshire bolus in the UK is evident from the results.

A few substitutes were mentioned once in the survey, including some home-made materials, the Rossi–Failla liquid (Rossi and Failla, 1956), Bakelite, "Melinex", "Plasticine", polyurethane foam, rape seed and "Vaseline-gauze". Surprisingly the excellent conducting plastics of Shonka (Shonka *et al.*, 1958) are only used by one of the 90 centres.

A number of participants indicated that existing available substitutes do not cover the requirements of both present and future experimental work. Eleven centres said that substitutes which could be readily moulded, machined and perhaps re-used, are needed. A further eight thought that new low-cost materials are required, simulating a wider range of tissues than previously considered. Seven centres have a particular need for materials suitable for particulate radiation (electrons, neutrons and protons), while three more have requirements for better bolus materials.

ACKNOWLEDGMENTS

Professor R. Barke (Germany), Mme A. Dutreix (France), Dr. W. Herstel (Netherlands), Dr. T. Hiraoka (Japan) and Dr. Per-Olov Löfroth (Sweden) are acknowledged for their

1977, *British Journal of Radiology*, *50*, 604–606

TABLE I

The results of the survey

Country	France	Germany	Hungary	Japan	Netherlands	South Africa	Sweden	U.K.	Misc.	Total
No. of centres	5	15	3	6	6	4	5	36	10	90
Body phantoms	No. of centres using body Phantoms									
Alderson	3	7	1	3	4	2	3	1	9	33
Homemade	2	9	1	4	1	1	3	5	1	27
Temex	—	—	—	1	1	—	—	13	—	15
3M	—	—	—	—	—	1	—	1	—	2
Water/Shell	—	7	2	1	1	—	—	5	2	18
Materials	No. of centres using tissue substitute materials									
Aluminium	—	—	—	1	—	—	—	3	—	4
Cork	—	1	1	2	—	—	—	—	—	4
Lincolnshire bolus	—	—	—	—	—	2	—	21	—	23
M3	—	3	—	—	—	—	—	—	—	3
Mix D	—	2	1	5	—	2	3	19	2	34
Nylon	—	1	—	1	—	—	—	—	—	2
Perspex	3	3	1	—	—	2	1	11	4	25
Polyethylene	—	—	—	—	1	—	—	3	—	4
Polystyrene	3	5	—	1	1	1	5	8	6	30
Pressdwood	—	—	1	—	1	1	—	12	2	17
Rice	—	—	—	—	1	—	—	—	4	5
Temex	—	2	—	—	3	2	—	17	—	24
Water	2	10	2	2	3	1	3	24	4	51
Wax	2	7	—	1	2	3	1	15	4	35

co-operation in distributing questionnaires to relevant centres in their own countries.

Yours etc.,
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The Editor—Sir,

Radiosensitivity of Melanoma Cells in Culture: Implications for Radiotherapy of Malignant Melanoma

Malignant melanoma has been considered a radioresistant tumour (Rock-Carling *et al.*, 1955). The radioresistance has been attributed primarily to the unusually large shoulder reported with X or γ-radiation for *in vitro* survival curves by Barranco *et al.* (1971) and Thomson *et al.* (1975) for human melanoma cells and Dewey (1971) for Hardin-Passey mouse melanoma. A "high-individual-dose fractionation schedule" would be expected to give better therapeutic results for tumours whose cells exhibit a large shoulder in their survival curves. On the basis of his nominal standard dose concept and using extrapolation number, $n = 25$, and $D_0 = 85$ rad for survival curves of melanoma cells, Ellis (1974) estimated that a great improvement would be expected in the sterilization of malignant melanoma by the use of a small number of large doses (7 × 620 rad) as compared to a large number of small doses (31 × 200 rad). Based on the large extrapolation numbers reported for melanoma cells irradiated *in vitro*, Habermalz and Fischer (1976) initiated a clinical trial with high individual treatment doses on patients with malignant melanoma.

A recent *in vitro* radiosensitivity study suggested that not all malignant melanoma cells give survival curves with unusually large shoulders. Malaise *et al.* (1975) reported n and D_0 values for survival curves for three different cell lines derived from human melanoma which differed little from those for other cultured mammalian cells. The cells used in these experiments were shown to be tumorigenic by the 80–90% "takes" on injection of 10^6 cells into athymic mice.

In this communication, we report finding small extrapolation numbers from data obtained with mouse melanoma cells. The highly pigmented clone, B$_5$59, derived by Silagi (1969) from B16 mouse melanoma, was used to obtain the survival data. Methods of cell culture and medium (Eagle's minimal medium with 10% fetal bovine serum) used were the same as previously described (Silagi, 1969). Log phase cells, removed from plastic flasks by trypsinization, were irradiated as "single-cell" suspensions in a calcium-free medium in sealed glass ampoules as previously reported by Zeitz *et al.* (1975). Oxygenated sparse cultures (10^5 cells/ml), maintained at room temperature, were continually mixed during irradiation with ^{60}Co γ rays at a dose rate of 100 rad/min. The cells were prepared for colony counting by plating appropriately diluted irradiated samples into 60 mm plastic petri dishes, incubating for 14 days, and staining with crystal violet after a two-hour period in 10% formalin.

The B$_5$59 cells have been consistently shown to be tumourigenic by producing tumours in 100% of C57BL/6J mice in two to three weeks after injection (s.c.) of 2×10^5 to 10^6 viable cells (Silagi and Bruce, 1970; Wrathall *et al.*, 1975).

The non-linear least squares method (CURFIT) of Bevington (1969) was used to fit the data of Fig. 1 to the function $S = 1 - (1 - e^{-D/D_0})^n$ where D_0 and n are the derived parameters which characterize the data. The uncertainties are standard errors as defined by Bevington (1969), and are based on a ± 10% error expected in the colony counting and a ± 1% error in dose. The n value of 1.7 ± 0.4 found for the B$_5$59 cells in this experiment was repeated in seven others carried out over an eight-month period, where the range was from 1.5 to 1.8 and the mean $(\bar{n}) \pm 1$ standard deviation (σ) was 1.6 ± 0.2. The mean quasi-threshold dose, D_q, was 101 ± 11 rad. The plating efficiencies in these experiments varied from 19 to 40%. For purposes of comparison, it is worth noting that HeLa-S3 cells harvested at near-confluency and treated in a manner identical to that described above, and previously reported by Zeitz *et al.* (1975), gave a range of n values from 2.0 to 2.7 ($\bar{n} \pm \sigma$ of 2.4 ± 0.3) in four experiments done over almost a two-year period and $\bar{D}_q$ of 120 ± 10. The plating efficiencies varied from 60 to 75%.

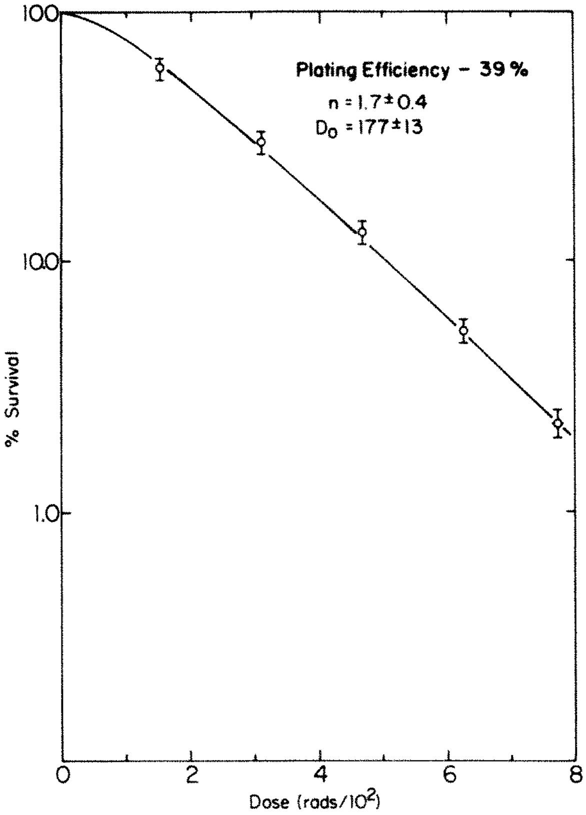

FIG. 1.

Survival curve for mouse melanotic melanoma cells, B$_5$59, irradiated as sparse "single-cell" suspensions under oxic conditions with ^{60}Co γ-radiation.

The D_0 values in the eight experiments with B$_5$59 cells had a range of 158 to 200 rad with $\bar{D}_0 \pm \sigma$ of 189 ± 14 rad, significantly higher than that found for HeLa-S3 cells where the range was 127 to 140 rad with a mean of 133 ± 7 rad for the four experiments.

These data, as well as those of Malaise *et al.* (1975), suggest that not all malignant melanoma cells show large shoulders in the *in vitro* survival curves produced with low linear energy transfer radiations such as orthovoltage X-rays or γ rays.

These reported differences deserve further evaluation. If found to be meaningful and reproducible, the basis upon which Habermalz and Fischer (1976) proposed to use a fractionation schedule with large individual doses in the treatment of human melanoma would have to be reassessed.

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ACKNOWLEDGMENTS

We wish to thank Drs. J. H. Kim, J. S. Laughlin, and J. Wrathall for helpful discussions, and Ms. G. Dymbort for technical assistance. This work is supported in part by NCI Grant No. CA-08748.

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THE EDITOR—SIR,

RESTRICTED APPLICABILITY OF THE "TEN-DAY RULE"

There has been interminable discussion of, and correspondence on, the so-called "Ten-day Rule" (BRITISH JOURNAL OF RADIOLOGY, 1973) since it was first enunciated by ICRP (1962). Consideration has been given to its implementation over a wide field of radiation medicine, including diagnostic radiology (HMSO, 1972), dental radiology (DHSS, 1975), and nuclear medicine (Sear, 1974). It is perhaps worth recalling that in their report, ICRP introduced three related modifications to their previous recommendations.

1. The maximum permissible dose to gonads and blood-forming organs had been 5 rem per year so long as not more than 3 rem was received in a 13-week period; the receipt of a single dose of 3 rem had been deprecated but not excluded. In 1962, the 13-week figure (and therefore the maximum single dose) was reduced to 1·3 rem for women of reproductive age (later changed to reproductive capacity).

2. An additional requirement for an occupationally-exposed woman who became pregnant was that the average dose to the fetus during the remainder of the pregnancy should not exceed 1 rem, with no prohibition of this being received as a single dose.

3. The "Ten-day Rule", that radiological examinations of the lower abdomen and pelvis of women of reproductive age, but not of importance in connection with the immediate illness of the patient, be limited to the ten-day interval following the onset of menstruation when pregnancy is most improbable.

Points 1 and 2 above suggest that ICRP envisage the risk associated with a dose of up to about 1 rem to a fetus of any age as acceptable. It appears, therefore, that ICRP intended the "Ten-day Rule" to apply in situations where an early fetus could receive a dose of more than about 1 rem in circumstances where, if the examination were postponed, medical care would not suffer. This is not inconsistent with a value of 0·5 rem deduced by Sear (1974) from a study of ICRP publication 16 (1970). If this interpretation is correct, it follows that this "Ten-day Rule" need not be implemented in diagnostic radiology where only scattered radiation will reach a fetus, as only under extreme conditions could this ever approach 1 rem. Further, in view of the depth of the uterus below the skin, a skin dose of 10 rem under normal radiographic conditions would be necessary to give 1 rem to the early fetus, and this will almost always involve several radiographs, or several minutes of fluoroscopy, with the uterus in the primary beam. The types of examination in which the "Ten-day Rule" needs to be implemented are therefore restricted, as is recognized by the recommendations of the Royal College of Radiologists (1976).

It is probably too late to put the clock back; for instance, women will no doubt continue to expect to be presented with lead-rubber aprons whenever they have teeth radiographed, and this will cause no harm. Such precautions can, however, hardly be justified by invoking the ICRP "Ten-day Rule".

Yours, etc.,
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THE EDITOR—SIR,

DYNAMIC BLADDER STUDIES IN CHILDREN

In his editorial on dynamic bladder studies (*British Journal of Radiology, 49*, 1976) Dr. Sherwood clearly distinguished between adult and paediatric investigations and mentioned the aptness of the MCU to the questions commonly raised in paediatric urology.

It would have been a good opportunity at this point in his editorial to have reminded readers of the importance of radionuclide cystography (RNC) as a complementary investigation for the children he describes.

As the radiation dose to the child's bladder during RNC can be up to one hundred times less than for an MCU, may we take the opportunity of reminding radiologists and clinicians that their protocol in the investigation of vesicoureteric reflux should not overlook this simple test. The dose advantage of RNC becomes particularly noticeable when the child is uncooperative during MCU, requiring multiple X-ray exposures.

Direct (per catheter) radionuclide cystography used alongside conventional radiographic techniques according to a carefully planned protocol (Rothwell *et al.*, 1977) during the medical and surgical management of these children should, we feel, be much more widely used than it is at present in this country. RNC can be performed at low cost, can frequently result in accurate determinations of residual urine volumes and need not expose the child to a bladder radiation dose exceeding 15 to 30 mrad.

Yours, etc.,
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REFERENCE

ROTHWELL, D. L., CONSTABLE, A. R., and ALBRECHT, M., 1977. Radionuclide cystography in the investigation of vesicoureteric reflux in children. *Lancet, 1*, 1072–1075.

Correspondence

THE EDITOR—SIR,

CHIBA NEEDLE PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY

We welcome the excellent review of Chiba needle percutaneous transhepatic cholangiography (PTC) (Jain *et al.*, 1977).

We would make the following points based on our experience of this technique here and at Sefton General Hospital (47 attempts, 39 successful, eight undilated, 31 dilated).

1. Barium examination of the duodenum immediately following the cholangiogram greatly improves anatomical orientation.
2. We have not encountered cholangitis or septicaemia as a complication although we do not aspirate bile or use antibiotic cover.
3. Failure to operate within hours of a PTC diagnosis of extra hepatic obstruction has not lead to trouble. These patients are operated on electively, often after an interval of some days.

Yours, etc.,
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REFERENCE

JAIN, S., LONG, R. G., SCOTT, J., DICK, R., and SHERLOCK, S., 1977. Percutaneous transhepatic cholangiography using the "Chiba" needle—80 cases. *The British Journal of Radiology*, *50*, 175–180.

Book review

Dynamic Radiology of the Abdomen—Normal and Pathologic Anatomy. By Morton A. Meyers, pp. 351, 1976 (New York, Heidelberg, Berlin, Springer-Verlag), DM72.80.

Radiology of the Abdomen: Anatomic Basis. By Joseph P. Whalen, pp. 310, 1976 (Philadelphia, Lea & Febiger; Britain Henry Kimpton), £22·10.

Joint reviews of books on the same subject are well established in general journalism. It seemed right to grasp a similar nettle for this journal since many libraries and individuals will have to make a choice between these two books.

They are both excellent. Visitors to medical schools in the United States must be impressed that the plain film of the abdomen is often squeezed much harder there than here. There may be a lingering complacent suspicion that the clinical pay-off from such study is slight, however beautiful the radiological dissection of the film. I do not think this *laissez-faire* attitude will do. It discourages efforts at understanding *in vivo* anatomy of the abdomen. The books by Meyers and Whalen show that this anatomy is not easy, but that it is very rewarding and can be learnt readily when there are such brilliant tutors to hand.

The inspiration behind both books is cross-sectional anatomy as revealed in cadaver slices. Indeed, there are beautiful, identical plates of such sections in these volumes. Building up a three-dimensional picture of normal and morbid anatomy from multiple cross-sections is of obvious, immediate relevance to understanding computed tomography. Both books have illustrations of this technique as well as ultrasound scans.

Dr. Meyers' book *Dynamic Radiology of the Abdomen* is the more lavishly produced, with anatomical colour plates and a very careful general lay-out. In keeping with its title the volume is particularly concerned with dynamic features. There are illuminating sections on the movement of fluid in the peritoneal and extraperitoneal spaces in order to understand how such collections and infective processes spread and localize. One chapter deals with contrast examination of the peritoneum, again emphasizing dynamic aspects. The presentation throughout is a model of clarity and care.

The publishers have not served Dr. Whalen quite so well in his book *Radiology of the Abdomen: Anatomic Basis.* In particular, the distancing of radiographs from the relevant text is really troublesome. Page after page of text on the colon, for instance, is illustrated by upper G.I. tract pictures belonging to the previous section. I think this is more than just a reviewer's grouse—it is the reader who is put off. To set against this there are excellent ideas. The fact that the splenic flexure is somewhere quite different from its place in popular teaching, that the palpating hand delineates anterior (peritoneal) borders of organs where the radiologist's eye sees their posterior (retroperitoneal) contours—there are insights of splendid simplicity and everyday relevance on many pages. Readers may not take as readily to other proposals, for instance for naming sections of the colon by number. Dr. Whalen is particularly good on the localization of abdominal masses, using the notion of vectors to judge displaced structures.

I think these are both fine books, and not only for those few departments with whole body C.T. scanners. Interpreting films of the abdomen is one of the most difficult tasks facing the trainee radiologist, and most training departments will probably wish to own one of these books. Ideally they might well like to have both, but in hard times it must be said that these volumes are similar in aim and subject matter. I know which I like best, but it would be invidiously unfair to single out one or the other here. I suggest that interested purchasers obtain each book on approval in order to compare and choose. It will be a sorry or a very talented department indeed which turns down both.

THOMAS SHERWOOD.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

B.I.R. LIBRARY

The opening of the Institute's house for members to use the Library on Saturday mornings has been discontinued through lack of support. However, arrangements would be made for the Library to be opened between 10.00 a.m. and 1.00 p.m. on a Saturday if prior notice was given. Telephone 01–935 6237 or write to The General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

INTERNATIONAL DIRECTORY OF SPECIALIZED CANCER RESEARCH AND TREATMENT ESTABLISHMENTS

UICC wish to announce the availability of the UICC Calendar of International Meetings on Cancer. It appears three to four times per year and can be obtained free of charge from International Union Against Cancer, rue du Conseil-Général, 3 1205 Geneva, Switzerland.

HYPOXIC CELL SENSITIZERS IN RADIOBIOLOGY AND RADIOTHERAPY

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

SIXTH INTERNATIONAL CONFERENCE ON THE USE OF COMPUTERS IN RADIATION THERAPY

Will be held at Gottingen on September 18–23, 1977. Further information from: R. E. Bentley, Physics Department, Royal Marsden Hospital, Downs Road, Sutton, Surrey, or Professor U. Rosenow, Strahlenabteilung, Unit.-Frauenklinik, D-34 Gottingen, Fed. Rep. Germany.

XIV INTERNATIONAL CONGRESS OF RADIOLOGY

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV International Congress of Radiology, Avenida Churchill 97—5th Floor, ZC 39, 20,000, Rio de Janeiro, Brazil.

TUMOUR ULTRASOUND '77

An international symposium on the science and clinical practice of ultrasound diagnosis and localization of tumours will be held in London, on December 5–6, 1977. This has been arranged in conjunction with the Annual Scientific Meeting of the British Medical Ultrasonics Group which will be held on December 7–8, 1977 at the same venue. A commercial and scientific exhibition will be held throughout both meetings. It is intended that the meeting will give a systematic coverage of the field and that the published proceedings will provide an up to date view of the subject. For registration and abstract forms or further details write to Dr. Ralph McCready, Department of Nuclear Medicine and Ultrasound, Royal Marsden Hospital, Downs Road, Sutton, Surrey, U.K.

EUROPEAN SOCIETY OF NUCLEAR MEDICINE (2nd Congress on Nuclear Medicine)
with
THE BRITISH NUCLEAR MEDICINE SOCIETY (Sixth Annual Meeting)

Will be held at Imperial College, London, on April 17–19, 1978.

Papers are invited and abstracts should be submitted by December 1, 1977, on the special abstract forms obtainable from Dr. M. N. Maisey, Nuclear Medicine Department, Guy's Hospital, London, SE1.

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Receipt of the following book is acknowledged as a courtesy to the sender. This publication has been lodged in the Library of the British Institute of Radiology for the use of members.
Programme Radiation Protection. Commission of the European Communities Annual Report, pp. 623, 1976, £14·60.

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No. 3
Fundamental Aspects of Medical Thermography, by W. M. Park and B. L. Reece (1976) £3·40

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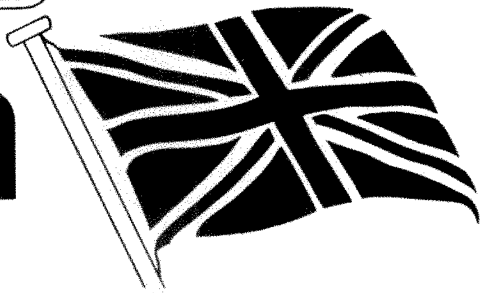

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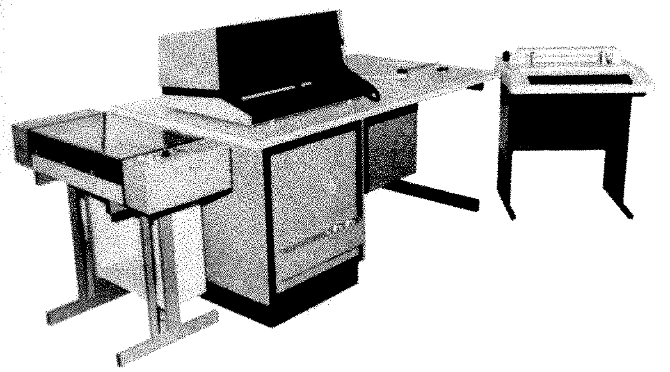

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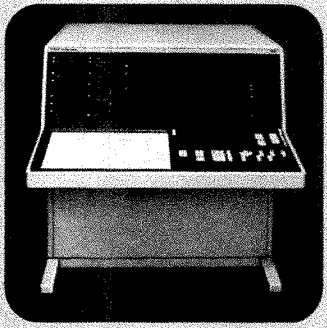

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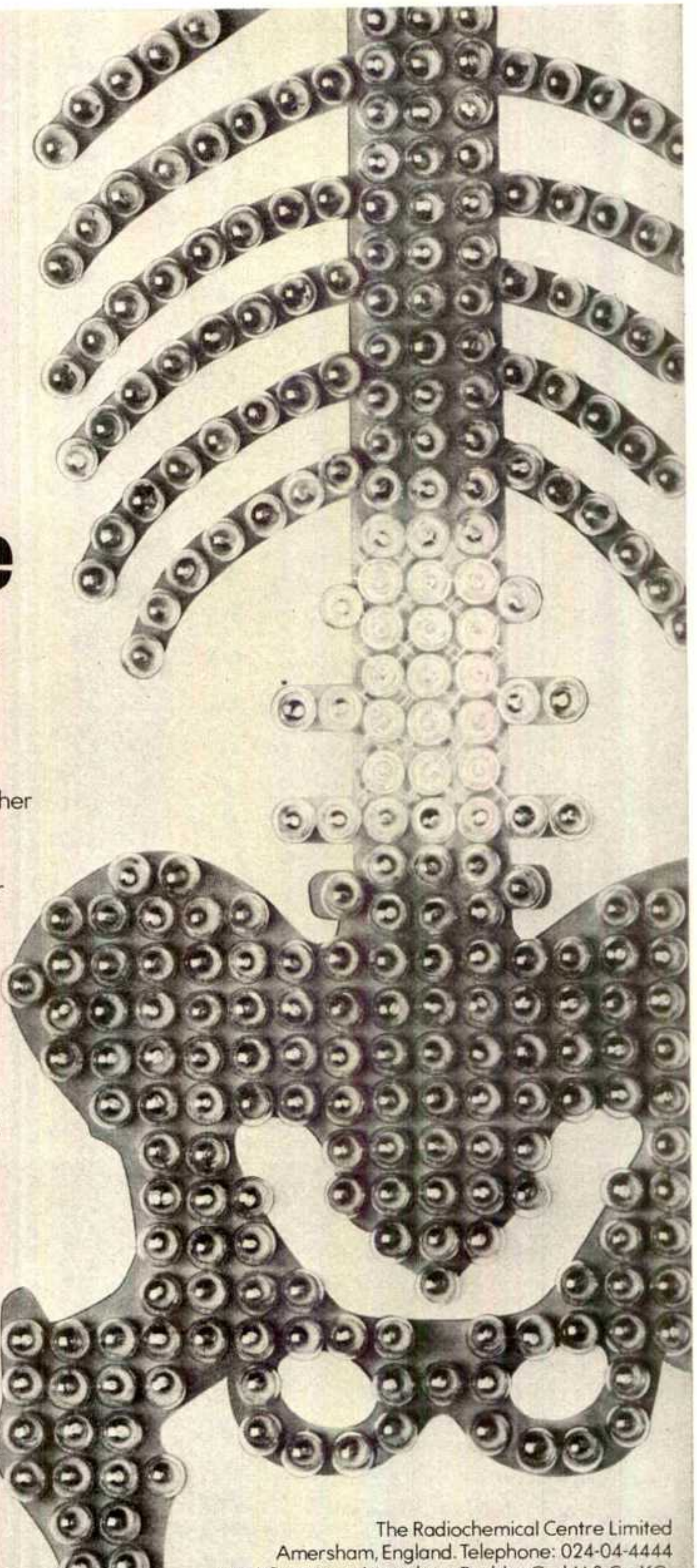

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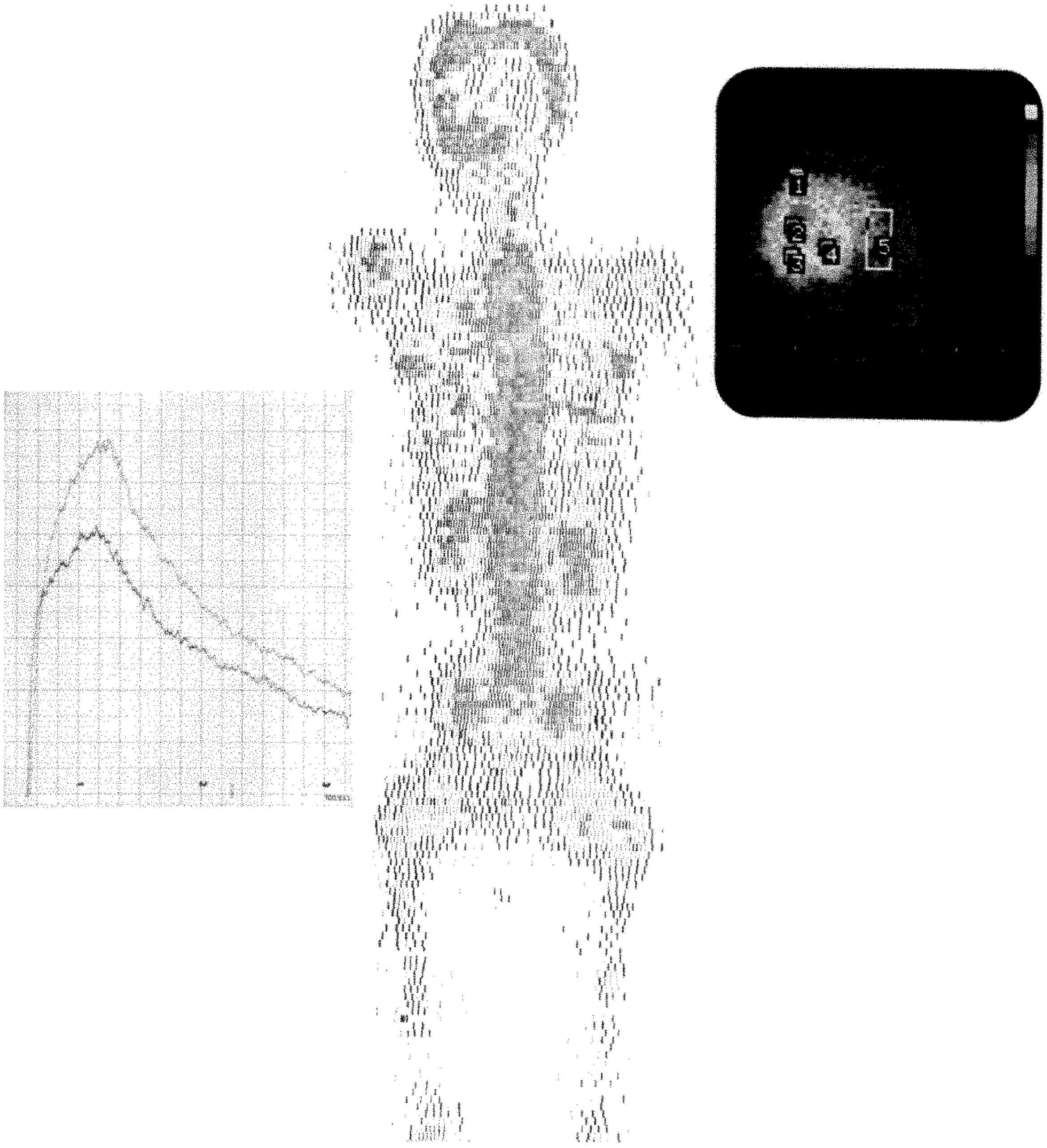

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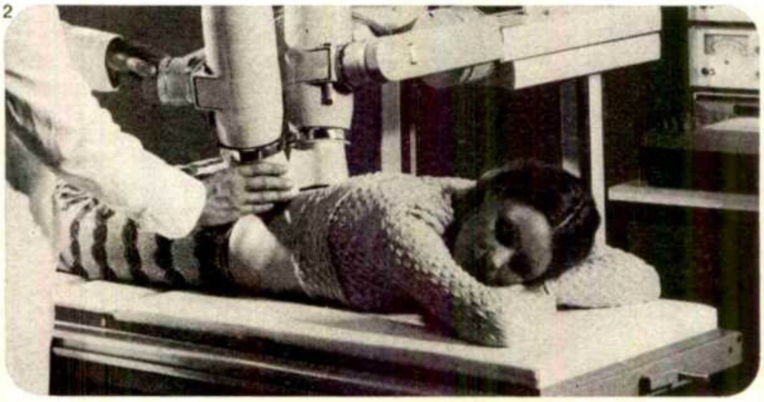

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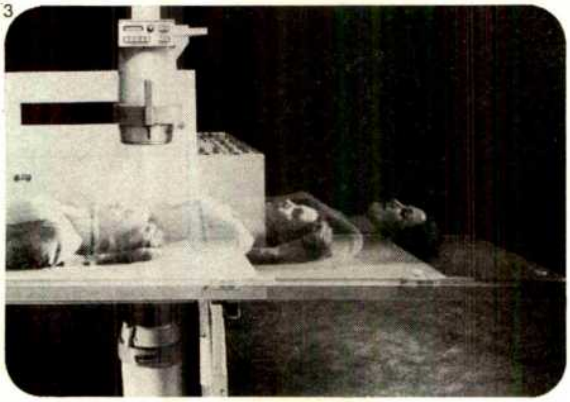

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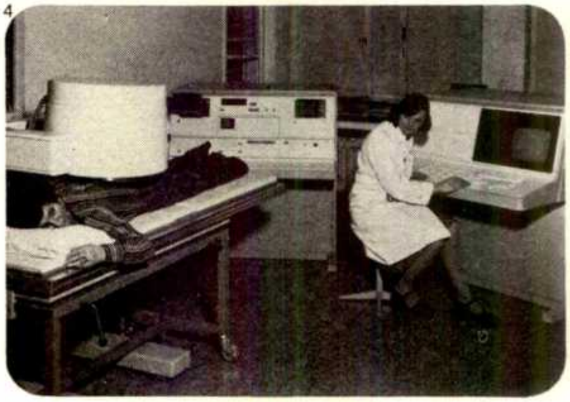

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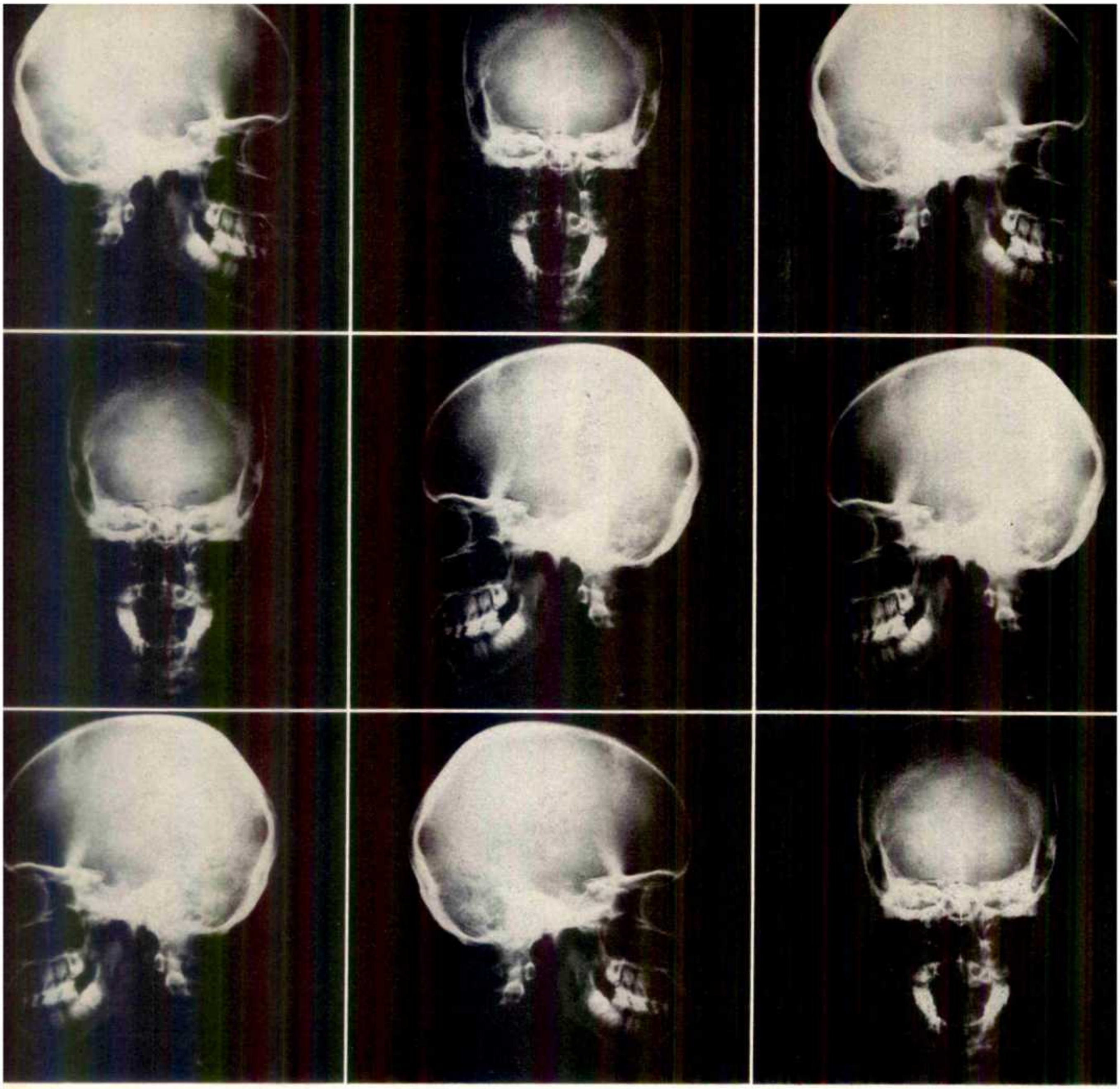

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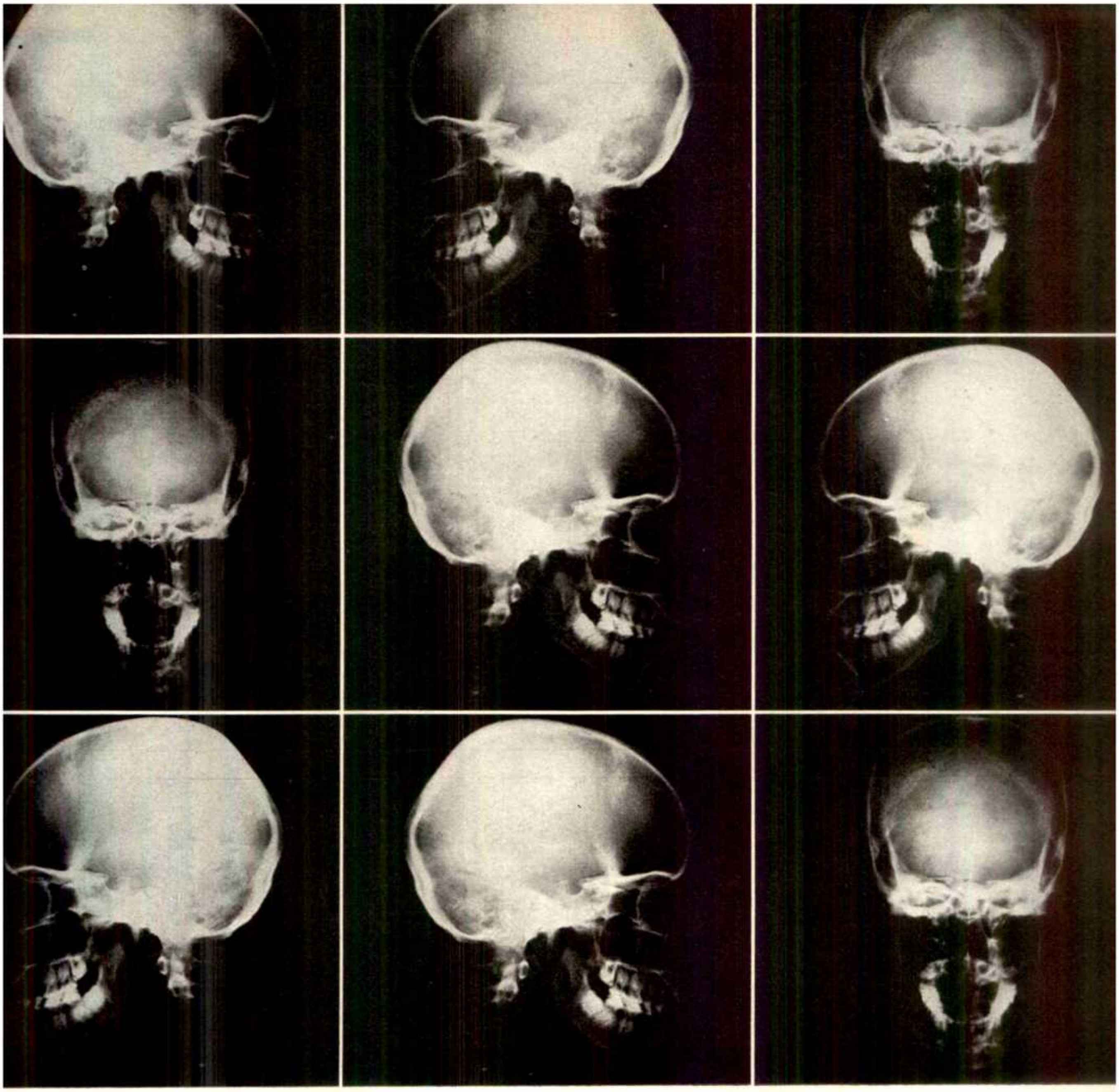

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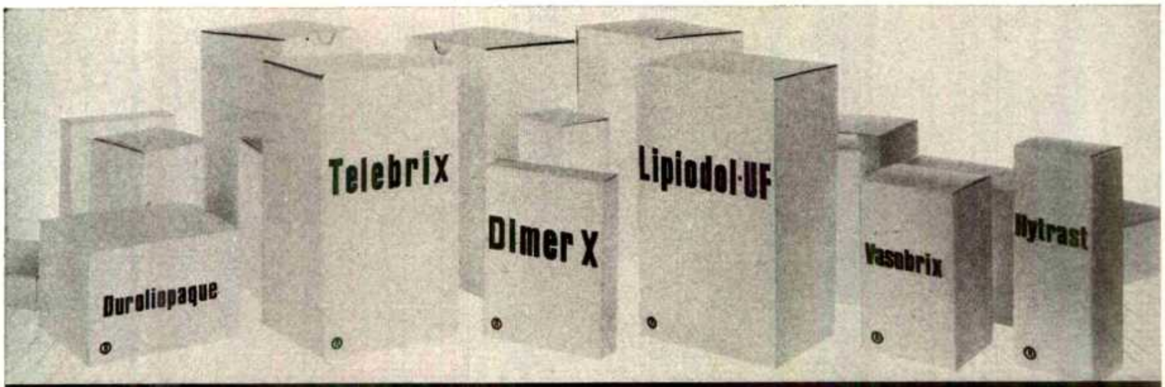

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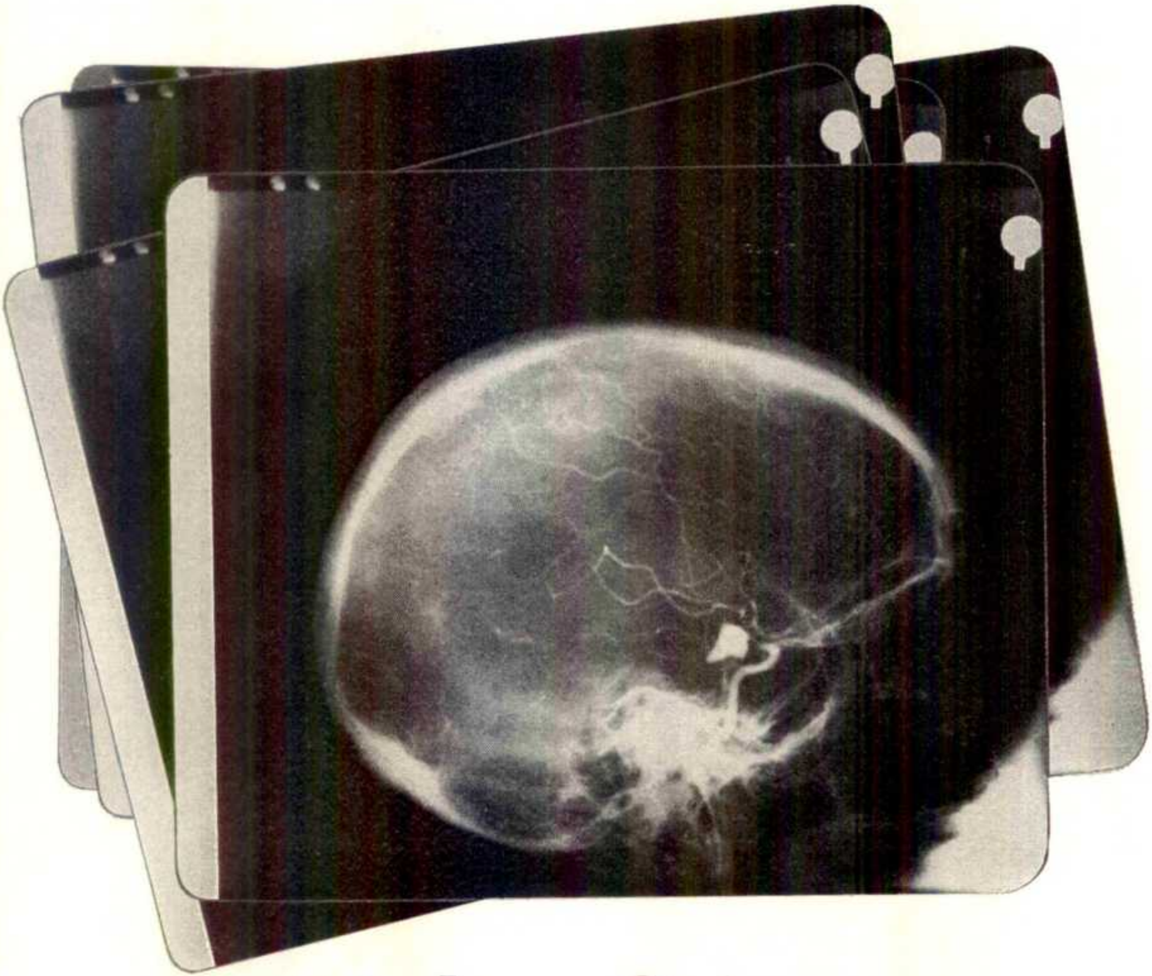

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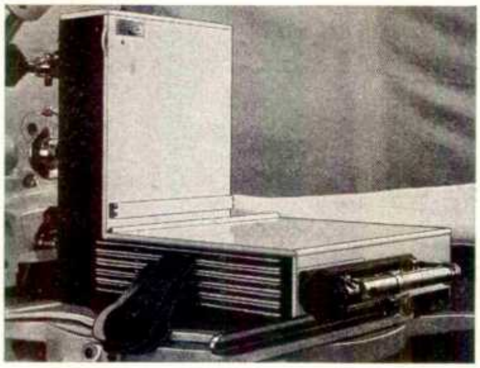

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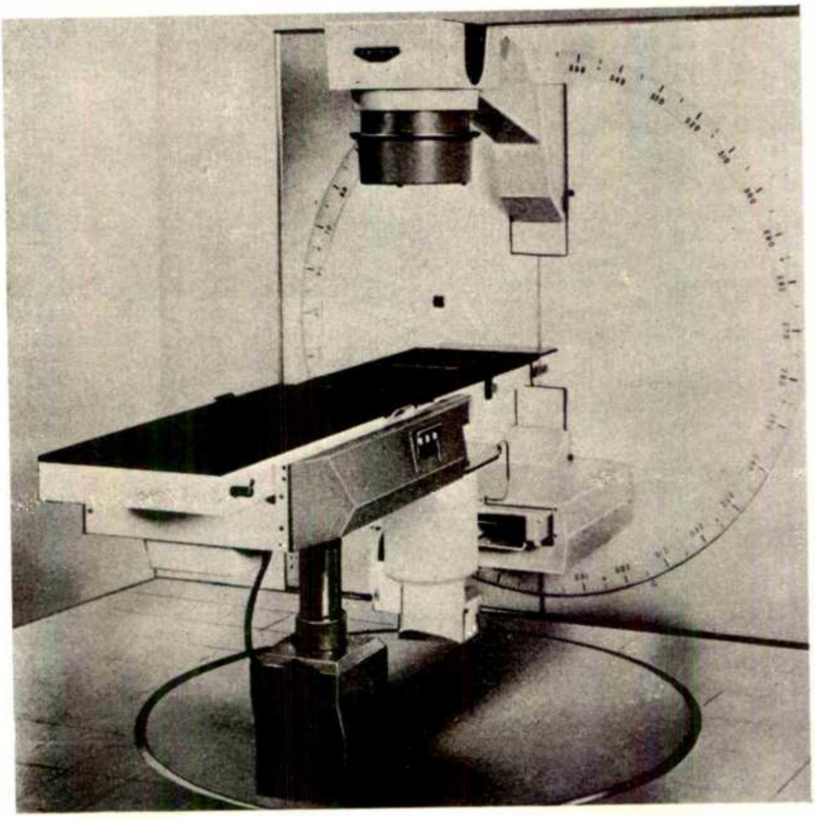

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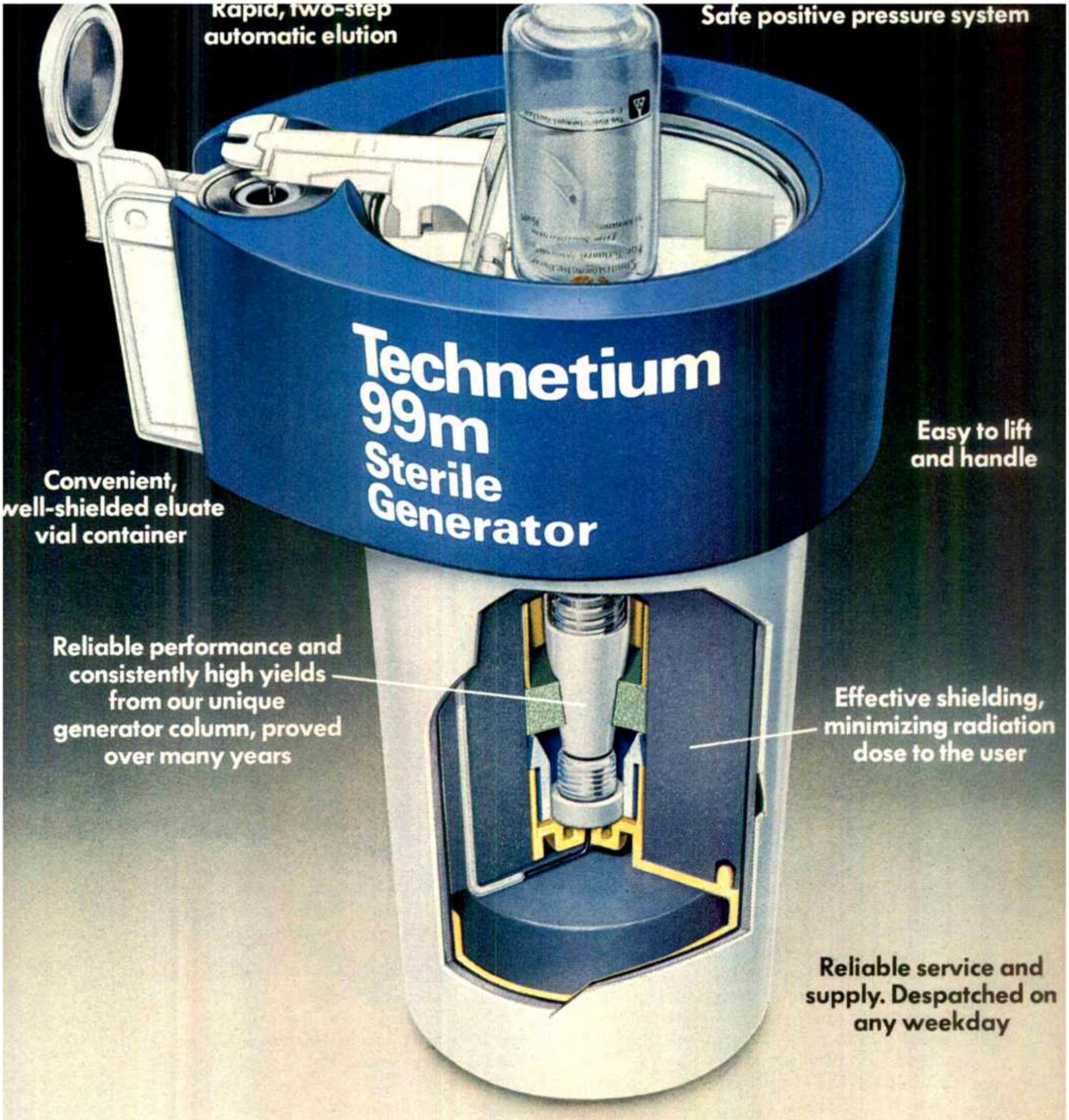
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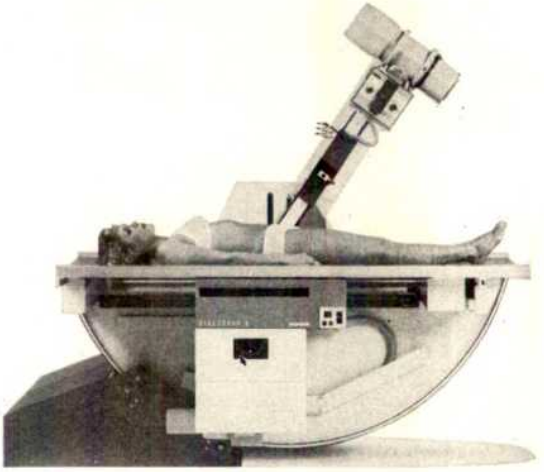

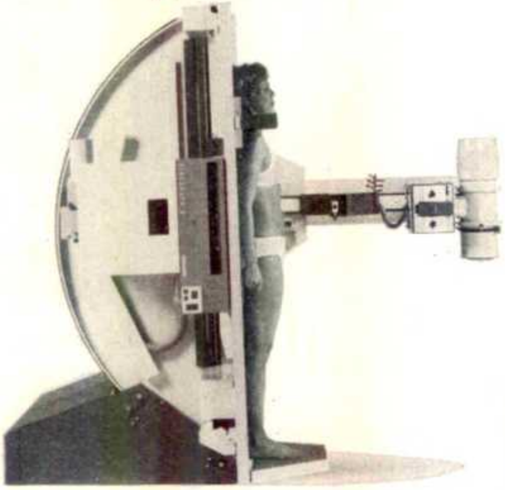

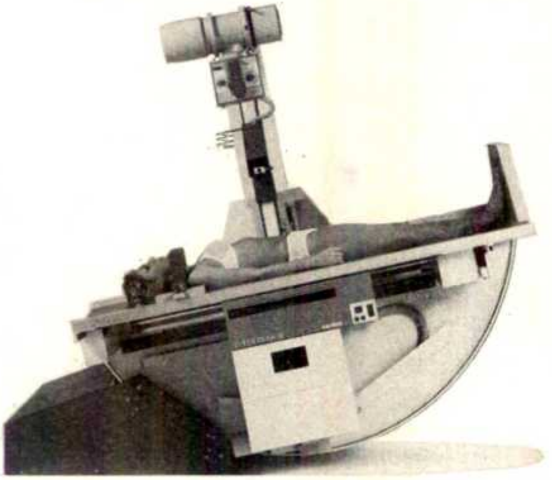

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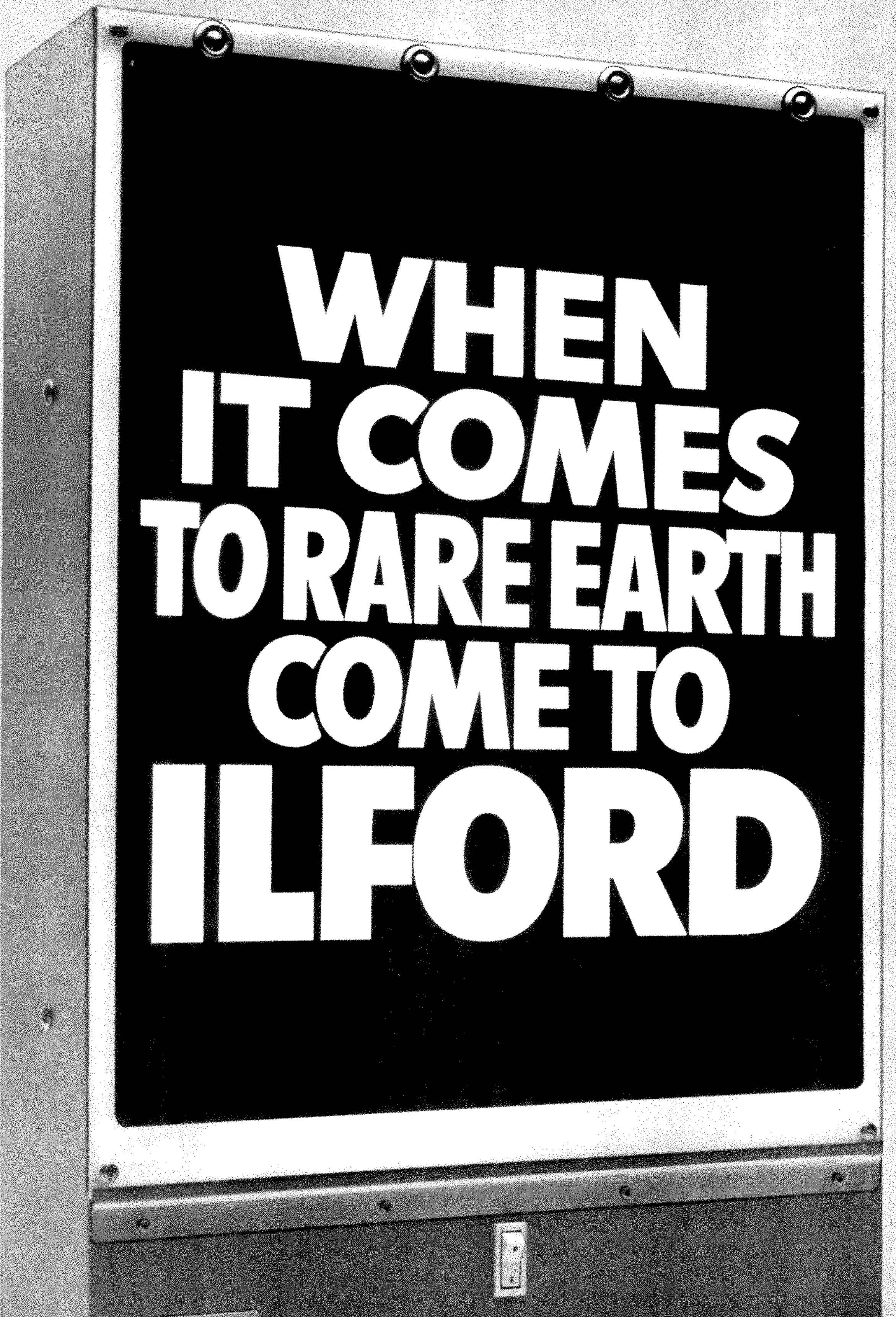
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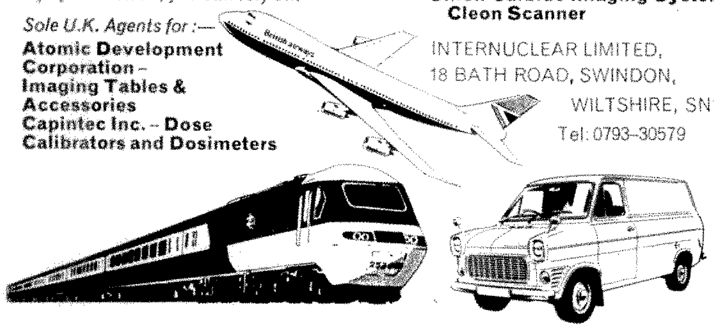

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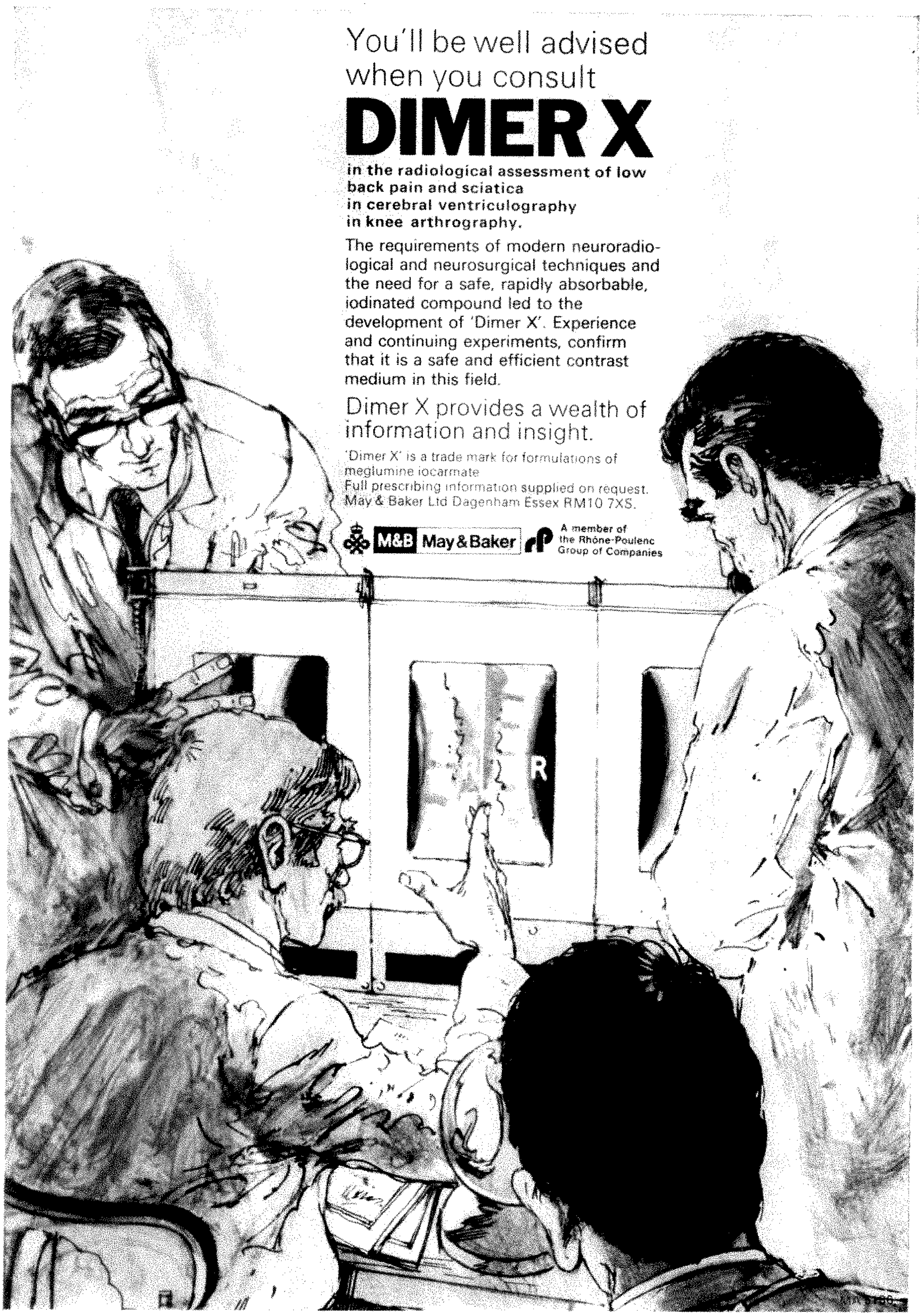

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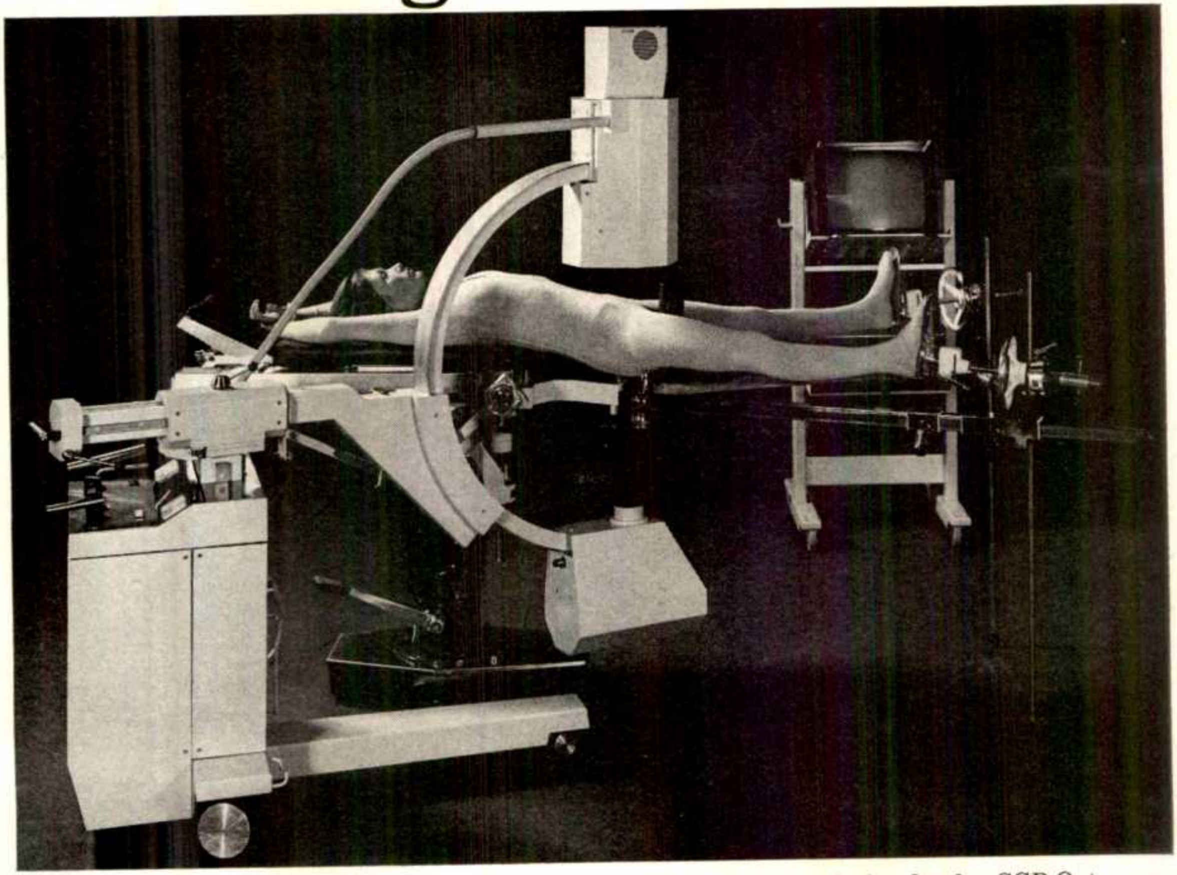

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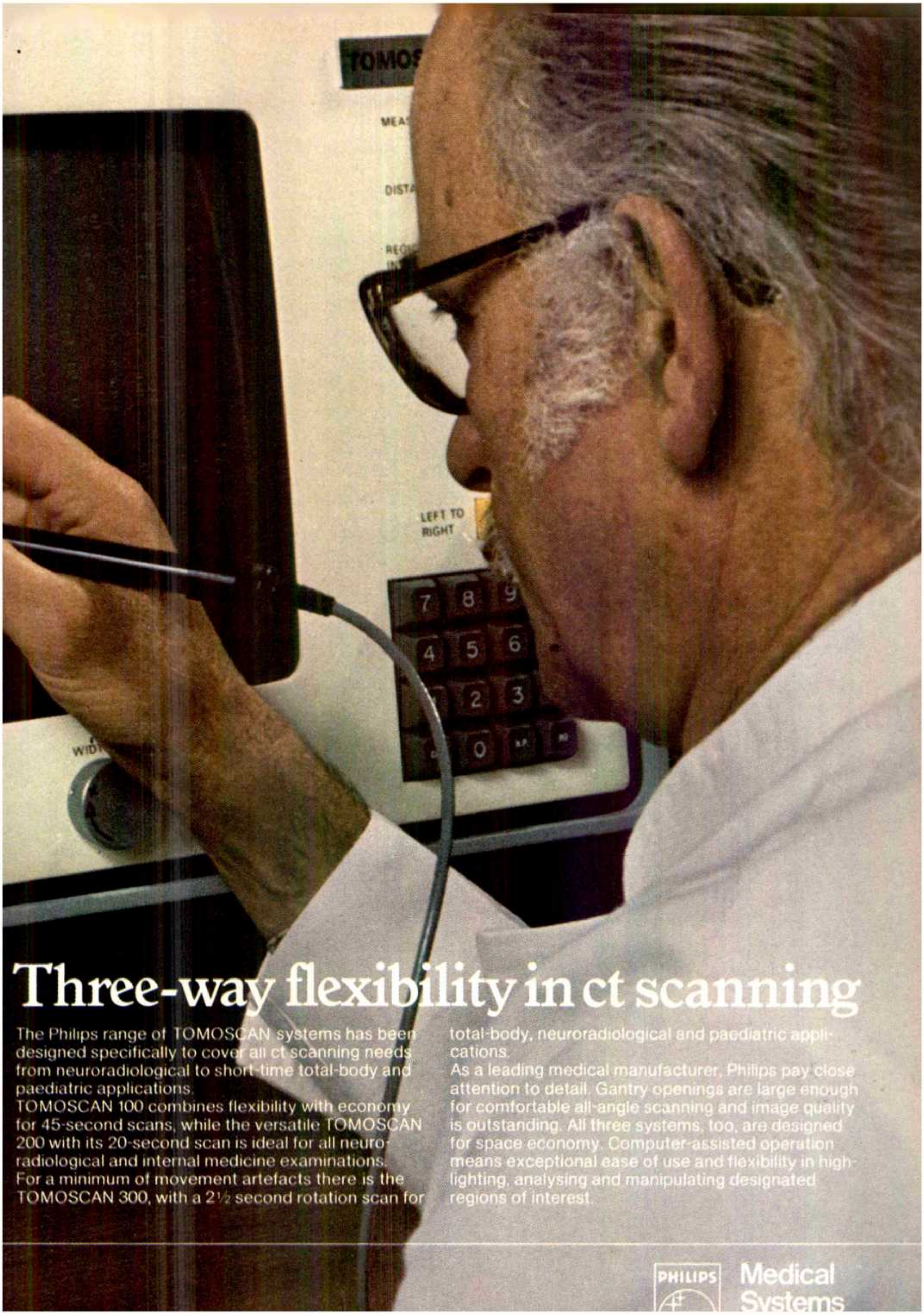

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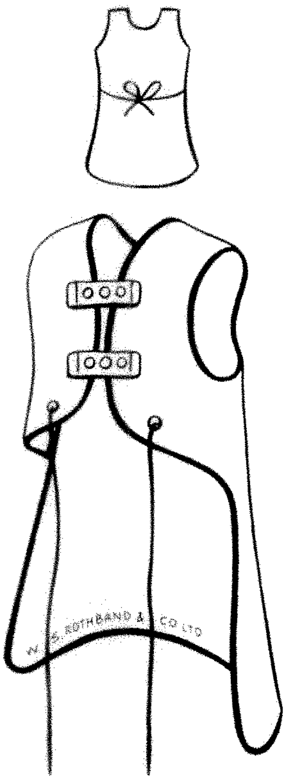
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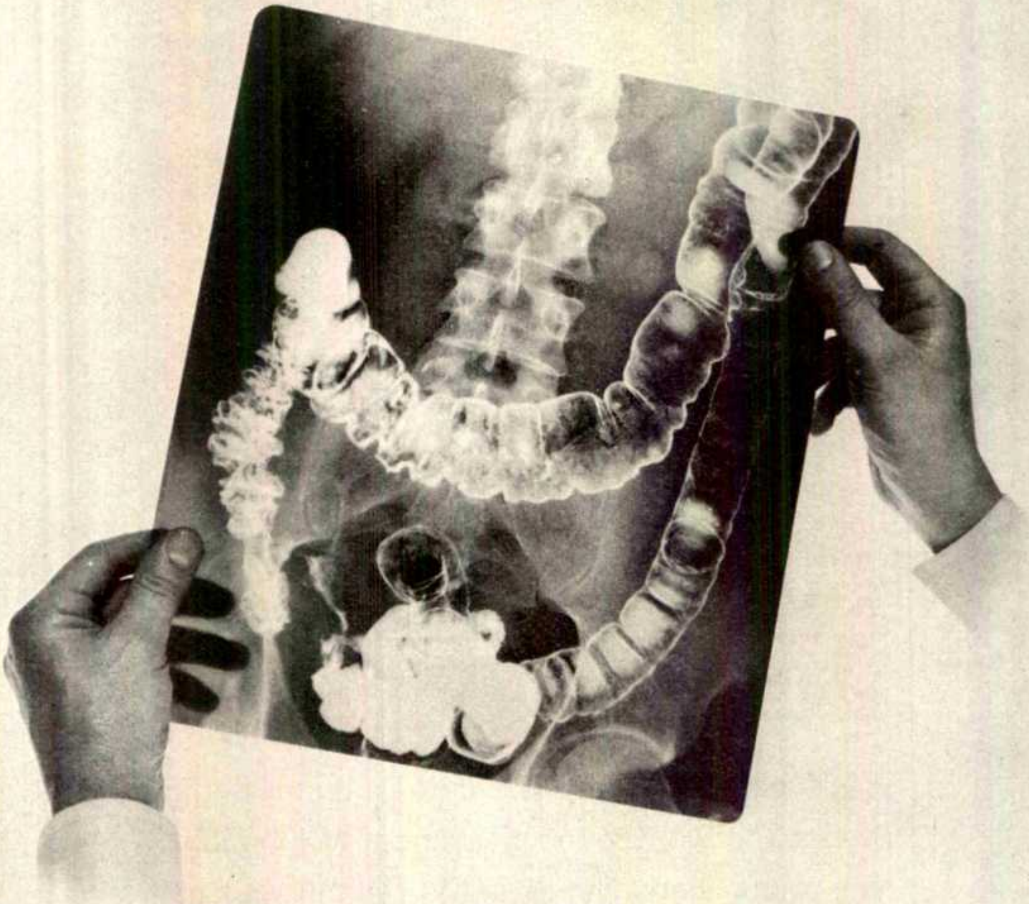

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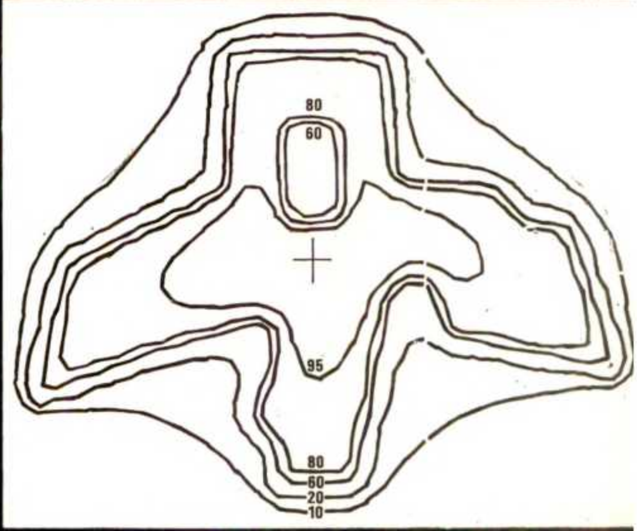

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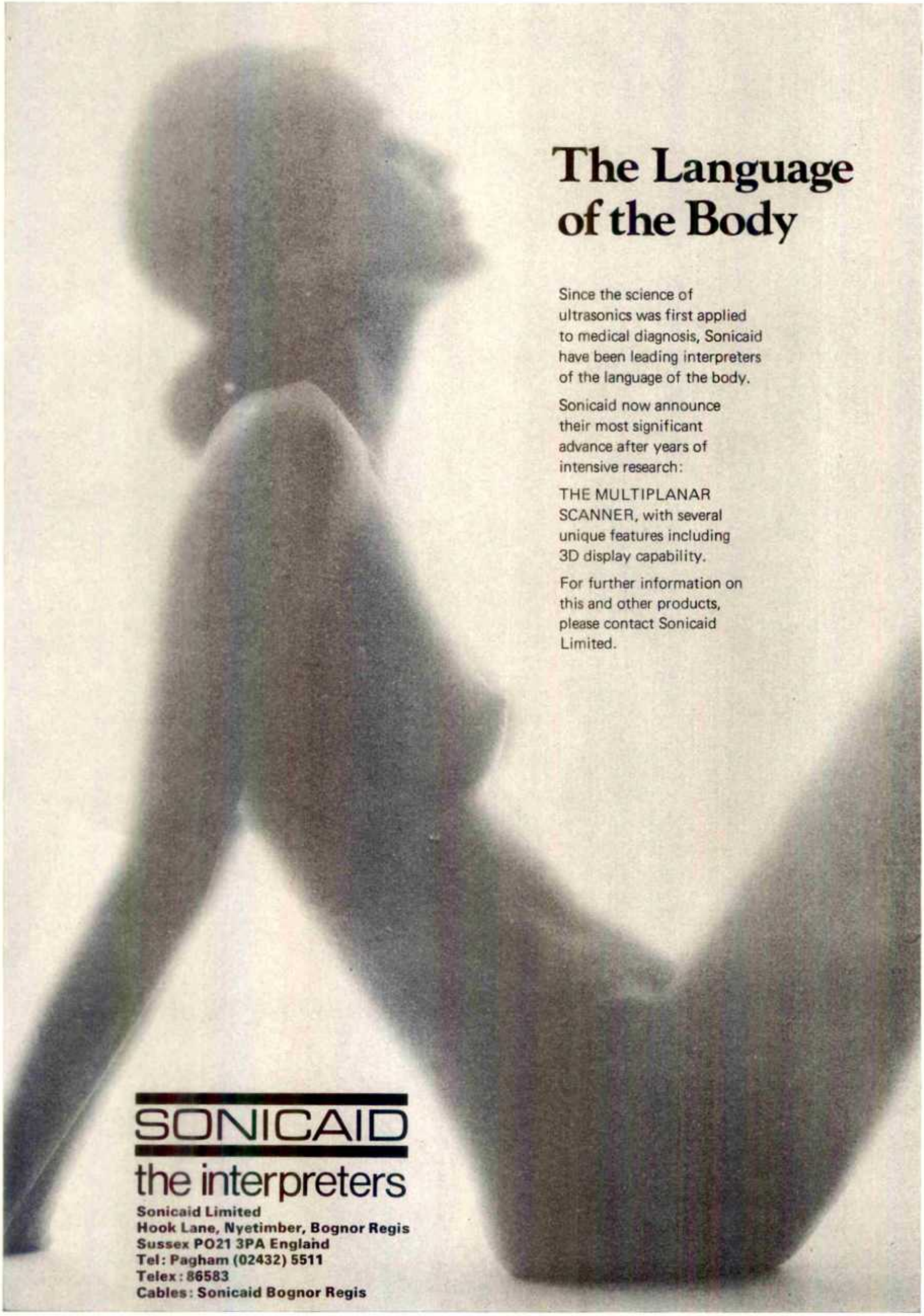

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Supplement No.13

British Journal of Radiology (1975)
Published by The British Institute of Radiology, 32 Welbeck Street,
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The Pathogenesis of Reflux Nephropathy

By Professor C. J. Hodson, F.R.C.P., F.R.C.R.,
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P. J. McManamon, M.B., B.Ch., L.G.M.C., F.R.C.R. and
M. G. Lewis, M.B., B.S., M.D., M.R.C.Path.

The association between vesico-ureteric reflux and renal damage has been recognized for some time, but it has usually been assumed that the damage is due to infection promoted by the reflux. However, observations by Rolleston and his colleagues in New Zealand have indicated a link between the severity of reflux and renal damage. Furthermore they have suggested that reflux penetrating into the renal substance is the factor most likely to explain the production of renal scarring.

These observations have been given a firm experimental basis by Professor Hodson and his associates. Their careful work on the growing pig has shown that the sites of intra-parenchymal or intra-renal reflux (I.R.R.) are the sites of subsequent scarring and atrophy. I.R.R. only occurs above a critical pressure level; reflux at lower-pressures produces no evident damage. Infection aggravates scarring, but in the presence of I.R.R., scarring can occur with sterile urine.

The work set out in this monograph has wide practical implications, and is of interest to paediatricians, nephrologists, urologists, radiologists and others concerned in the management of patients with urinary tract infection.

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1977, *British Journal of Radiology*, *50*, 609
VOLUME 50 NUMBER 597 SEPTEMBER 1977

The British Journal of Radiology

Editorial

Analysis of papers in the journal during 1976

The table below gives an analysis by subject of the contributions to the journal during 1976. The journal covers a wide range of subjects, as indicated on the front cover. Papers extending across the frontiers between subjects are a particularly noteworthy feature, reflecting the varied membership of The British Institute of Radiology which includes both medical and non-medical members on an equal footing. This, however, makes it difficult to allocate the papers in an objective way. In the table, papers put in interdisciplinary categories are those in which substantial parts relate to more than one category. All papers allocated to physics are of course concerned with the application of physics to some branch of radiology but in which the strictly medical component is small.

An analysis of this kind is to some extent subjective. It does, however, show that diagnosis with X rays (including case reports) accounts for rather under half the total, a similar position to that in other recent years. Diagnosis by all methods represents rather more than half the total. Radiotherapy represents a rather small fraction but much of the physics was physics applied to radiotherapy. Interdisciplinary papers are a significant fraction of the total.

D. K. BEWLEY

ANALYSIS OF PAPERS IN THE BRITISH JOURNAL OF RADIOLOGY DURING 1976
INCLUDING TECHNICAL NOTES AND CASE REPORTS BUT EXCLUDING SHORT COMMUNICATIONS, LETTERS TO THE EDITOR AND RADIOLOGY NOW

Category	Number of contributions	Number of pages	Pages per contribution	Per cent of total	
				contributions	pages
Diagnosis by X rays excluding case reports	47	295	6.3	28	34
Case reports (X ray diagnosis)	31	67	2.2	18	8
Diagnosis by ultrasonics	4	25	6.3	2	3
Diagnosis by nuclear medicine	9	50	5.6	5	6
Thermography	1	2	2.0	1	0
Radiotherapy	9	41	4.6	5	5
Physics	19	124	6.5	11	14
Radiobiology	13	79	6.1	8	9
Radiation hazards	3	19	6.3	2	2
Nuclear medicine with physics	13	63	4.8	8	7
X-ray diagnosis with physics	9	46	5.1	5	5
Radiotherapy with physics	3	12	4.0	2	1
Ultrasonics with others	5	25	5.0	3	3
Other combinations	3	22	7.3	2	3
Total	168	870	5.2	100	100

1977, *British Journal of Radiology*, *50*, 610–612

Radiology now

Starting the double contrast barium meal*

Many radiologists must be asking themselves whether they should use a double contrast barium meal (DCBM) as a routine. They may be tempted, as I have been, to make excuses—the added cost or the increased length of the examination. Yet standard barium techniques may miss 20 to 30% of endoscopically demonstrable abnormalities (Cotton, 1973; Laufer *et al.*, 1975) while at its best the DCBM has an accuracy comparable to that of endoscopy (Laufer *et al.*, 1975; Herlinger *et al.*, 1977). If a barium meal fails to show a potentially demonstrable lesion it may be doubly expensive and time consuming because of the unnecessary further investigations which ensue (de Lacey, 1977).

A major difficulty in adopting the DCBM is that it is by no means easy to work out a satisfactory and reliable personal routine and to obtain consistent results, in spite of the reviews of the technique which have been published (Kreel *et al.*, 1973; Laufer, 1975; Hunt and Anderson, 1976; de Lacey, 1977). Although not primarily a gastro-enterological radiologist I have, by degrees, become committed to the technique and hope, by discussing the problems, to encourage other radiologists to adopt it too. New diagnoses become possible and negative reports are given with greater confidence. Moreover a barium list, always a challenge, acquires a new interest, not least because almost every element in the technique is still under development and is open to experiment and improvement. Once a routine has become established the examination is not significantly longer than a standard barium meal. My own current routine will be outlined later after considering the different elements in the technique.

Preparation of the stomach

Gastric residues, whether due to secretion, food or saliva, may impair coating of the mucosa, and a reliable method of obtaining an empty stomach is needed. Some workers use preparatory metoclopramide but so far no controlled studies are forthcoming to indicate whether this is effective.

Gas Production

It requires 400–500 ml. of gas to distend the stomach fully in the routine examination of an average adult; less is usually required for patients who have had a gastrectomy. Gastric intubation is impractical for routine use and pace Scott-Harden (1976), carbonated drinks do not yield sufficient gas without an unacceptable volume of liquid. When effervescent tablets are used it is preferable to give them before the barium and wash them down with 25–30 ml. of water or anti-foaming agent, since the gas is then liberated more rapidly and bubble formation is reduced. Incompletely dissolved tablets or bubbles can sometimes be a problem, particularly if the volume of fluid is insufficient for complete dissolution of the tablets. Surprisingly, similar residues can occur with an alternative product—'Carbex"—where a sodium bicarbonate powder is swallowed first, followed by citric acid solution; probably the two components, given separately, do not always mix completely in the stomach. Whatever source of gas is used it should be compatible with the barium which otherwise may become excessively viscous (Hunt and Anderson, 1976).

Few patients find it pleasant to swallow effervescent tablets or powders but better alternatives are not available at present. Most individuals do succeed with some encouragement. All patients are told not to belch until the examination has been completed.

Barium

It is agreed that high density preparations ("Baritop", "Barosperse", "E–Z–Paque") are needed, but the factors which affect barium coating are still incompletely understood (Hunt and Anderson, 1976; Goodacre, 1976). It is evident that coating improves if barium is in contact with gastric mucosa for some time, and repeated "washings" with barium help to improve coating. Each film should, therefore, be taken immediately after barium has washed across the part of the stomach under examination. When a suspicious area is re-examined further rocking of the patient is desirable, if necessary after giving more barium.

Barium in cans is often shaken inadequately so that the concentration of the suspension may be variable. Use of barium powder avoids this difficulty. It appears that coating of the stomach is improved if barium is made up with distilled water rather than tap water (Denny, personal communication).

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Antifoaming agents

Agents such as simethicone and "Mylocon" do reduce bubble formation but they are not always used in a logical way. In "Baritop", for example, the tablets contain simethicone but the barium does not. In "E-Z-Paque", the barium contains simethicone which appears to be a more appropriate way of using it. Too high a concentration of antifoam can actually stabilize bubbles (Hunt and Anderson, 1976). It is clear that more work is needed on the best method of using these substances.

Hypotonic agents

Temporary paralysis is needed for full gastroduodenal distension; it also helps to prevent the rapid escape of gas and barium through the pylorus. Glucagon is too expensive for routine use, and in practice "Buscopan" is suitable for the great majority of patients. Its action is short-lived and although it is probable that patients should not drive a car while their accommodation is paralysed, this is seldom a problem after an hour. Workers in Belfast have obtained similar results using "Antrenyl" routinely with no difficulties from visual blurring (Gough, personal communication). Intramuscular injection of "Buscopan", if made before the gas producing agent is given, is as effective as intravenous injection and takes less time to administer. It has been suggested that the pylorus does not relax after "Buscopan" but experience does not confirm this. It is possible to obtain a satisfactory follow-through examination with normal transit time if the patient is given 25–30 mg of metoclopramide (as syrup) dissolved in 300 ml of water when the meal has been completed.

Interpretation

Use of the double contrast meal involves some adjustment in interpretation. The original purpose was the early detection of gastric cancer, and it is certainly useful to read the articles demonstrating such lesions. The main value in the U.K. is the increased accuracy in diagnosis of ulcers, scars and erosions. It must therefore be appreciated that ulcers on the anterior gastric or duodenal walls do not fill with barium in the supine position and that they are recognized as ring shadows with or without adjacent mucosal deformity. As in other branches of radiology, learning to interpret the films which one has obtained is a gradual process and lack of familiarity with the normal should not discourage radiologists from adopting the technique.

PROBLEMS

1. *Preventing gastric emptying*

An important film in the double contrast routine is the RAO supine view to show the mucosa in the gastric antrum and body. To obtain good coating of this region it must be filled with barium for some moments before the patient turns to the left side for this view. Yet if barium reaches the distal duodenum and jejunum it almost always overlaps the stomach. Various means have been suggested to prevent the stomach emptying too rapidly, usually involving antral or pyloric compression (Hunt and Anderson, 1976; de Lacey, 1977). Another method which has proved reliable is to give the barium while the patient lies on the left side, propped on his elbow. He is next rotated left side down and into the prone position and rocked from side to side. Then he turns partly on to the right side but as soon as any barium passes through the pylorus he is immediately rotated back through the prone and left side down position into the RAO position for the film to be taken.

2. *Anterior gastric wall*

Films of the stomach with the patient supine will not show detail of the anterior wall unless coating is excellent. This has led to the development of views which involve lying the patient prone, head down after a small volume of barium. High kV and a compression pad are often necessary (Hunt and Anderson, 1976); even then it is not always easy to demonstrate anterior wall mucosa in the lower half of the stomach. The upper half can usually be seen in a prone semi-erect film. The risk in omitting anterior wall views is chiefly of missing small neoplasms since it seems that anterior wall ulcers are relatively uncommon (Goldsmith *et al.*, 1976). Probably this view should not be used until the remainder of the routine has been mastered.

3. *Demonstration of the duodenal cap*

Although the duodenal loop is well shown and a double contrast duodenogram is routinely obtained, it is sometimes difficult to show the duodenal bulb properly because of overlying barium in the duodeno-jejunal flexure. This problem arises because the distended gastric body protrudes forward and the duodenal cap becomes more sagittally orientated. Sometimes the cap can be better shown with the patient in the semi-upright or near upright position, allowing barium to pull the stomach downwards, but in many such patients it is necessary to re-examine in 15–20 minutes, after the patient has belched.

4. *Age and immobility*

If a patient cannot turn easily or lie prone a true double contrast meal with good coating is seldom practicable and some form of compromise examination is inevitable.

5. *Gastric surgery*

After Polya and Billroth II forms of gastrectomy the patient lies on the right side while drinking barium. This helps to fill the afferent rather than the efferent loop. After gastro-enterostomy the stoma may be compressed to prevent rapid emptying (Hunt and Anderson, 1976), or the patient may drink the barium while lying tilted head down on the left side. A patient with a Billroth I gastrectomy is examined in a similar way to a normal stomach.

6. *Poor X-ray equipment*

The demonstration of fine mucosal detail requires good quality films. X-ray sets which will not produce sharp films give disappointing results and are unlikely to show small lesions such as erosions.

CONCLUSIONS

Although there are still many points of detail to be developed and improved in the double contrast technique, it is already a sensitive and accurate examination and should become the standard form of barium meal in this country. The single contrast barium meal has been left behind by endoscopy; radiologists must respond positively, in the only way at present available—by adopting the double contrast barium meal.

H. M. Saxton.

SUGGESTED ROUTINE

Note 1. "Clockwise" rotation means as viewed from below, *e.g.* supine patient turning on the left side.

2. "LAO", "RAO", "PA" etc., refer to position in relation to an under-couch tube.

1. After taking history from patient inject him with 20 mg Buscopan i-m. Warn against driving until vision normal.
2. Patient, sitting or standing, swallows 40 effervescent (*e.g.* "Baritop") tablets with 25 ml distilled water. Patient warned against belching.
3. Patient lies or is tilted into horizontal position: then rotates on to left side, supports himself on elbow to drink barium.

Optional *If prone anterior wall view is employed, he drinks 30 to 40 ml of barium and turns clockwise to lie on shallow pad placed to compress gastric body/antrum. Patient may need head-down tilt and/or slight counter clock-wise rotation.*

A.P. prone film. Patient then lies on left side again.

4. Patient drinks 150–200 ml barium and turns clockwise to lie prone; he rocks from side to side and turns slowly further clockwise half on to right side until barium enters pylorus. He then turns *rapidly* counter-clockwise into RAO position.
RAO supine film for gastric antrum and body.
5. Patient is next tilted supine head down and rotated half on to right side. Abdomen compressed to elicit possible reflux.

Optional *Films for hiatal hernia and reflux if required.*

6. Patient twice rotates counter-clockwise through 360° ending supine position, table horizontal.
P.A. supine film to show whole stomach and duodenum.
7. Patient rotates on to right side.
Lateral film of gastric fundus.
8. Patient rotates clockwise to LAO position allowing some barium to run across upper stomach into fundus.
LAO film of upper lesser curve.
9. Patient rotated further clockwise half on to left side.
RAO films to show duodenal bulb and loop and gastric antrum.
10. Patient turns into prone right side down position. Lies on compression pad and drinks barium through straw.

Optional *Oesophagus ± hiatal hernia views.*

11. Compression pad removed. Table tilted half upright.

Optional *Prone semi erect film of stomach.*

12. Patient lies on right side to fill duodenal bulb with barium, then turns clockwise to lie on his back as table is brought upright.
P.A. erect, stomach and duodenum
13. Patient turns half left to RAO position. Drinks more barium to coat lesser curve. Oesophagus observed fluoroscopically.
RAO erect stomach and duodenum
14. *Local compression films of duodenal cap*

Optional *Further "repeat" supine RAO films of duodenal cap may be obtained after belching if the cap has been masked on earlier films.*

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Electron density and atomic number determination by computed tomography

Part I: Methods and limitations
Part II: A study of colloid cysts

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ABSTRACT

The feasibility of extracting electron density and effective atomic number from measurements of tissue *in vitro* and *in vivo* has previously been reported. The method requires scans to be obtained at two different beam energies. Optimization of these energies at 40 keV and 80 keV could enable a variation of 1 part in 400 of effective atomic number to be detected. The method is subject to certain limitations related to accuracy and sensitivity. The effect of varying the concentrations of certain atoms has been modelled demonstrating the limits below which variation in effective atomic number is unlikely to be detectable at acceptable radiation doses.

A series of 12 patients with colloid cysts has been considered. All were treated by bilateral ventriculo-cisternostomy from one to 23 years ago. Nine of these patients, and the colloid cyst of one patient who died before treatment could be instituted, have been subjected to double energy scanning. The results suggest that the high attenuation values observed in colloid cysts are due to increased electron density and not to any increase in high atomic number elements. The cysts do not appear to change in size or content over long periods.

Computed tomography employing the EMI brain scanner (CT1000) is capable of precise measurements of the attenuation coefficient of small elements of tissue *in vivo* at X-ray voltages ranging from 100 kV to 140 kV. Substances whose densities differ by 1 part in 1000 can be differentiated (McCullough *et al.*, 1974; Rutherford *et al.*, 1976a.)

Despite the polychromatic nature of the X-ray beam, the computer algorithm implemented by the machine calculates attenuation values that relate linearly to the linear attenuation coefficient of the material at particular energies, *i.e.* 62 keV for the 100 kV beam, 70 keV for the 120 kV beam and 74 keV for the 140 kV beam (Rutherford *et al.*, 1976a).

Attenuation coefficients can be measured at two different beam energies and from such data it is possible to obtain separate measurements of electron density $N^* Z^*$ and effective atomic number, Z^*, of material (Rutherford *et al.*, 1976b). N^* is the effective number of atoms per unit volume. The effective atomic number Z^* is a measure of the mean composition of the material.

The validity of the method has been checked by comparing measured effective atomic number, Z^*, and electron density with similar values calculated for materials of known composition (Rutherford *et al.*, 1976b). A mean variation between actual and predicted values of atomic number, Z, was less than 1%.

The feasibility of extracting mean atomic number and electron density in the clinical situation has previously been investigated (Rutherford *et al.*, 1976b). In order to reduce noise, values of EMI number have been obtained by averaging over 25 elements progressively across the scan. Electron density determined in this way is accurate to ½% and the effective atomic number accurate to 3%. This disparity is due to the fact that at the beam energies currently employed the dominant interaction is Compton scattering which is an interaction between X rays and electrons and which therefore depends very little on the type of atom present.

Part I: Methods and limitations

Relevance of electron density and effective atomic number measurement

Certain questions need to be considered if the measurement of electron density and Z^* is to prove a worthwhile application of computed tomography.

(A) Physical.

1. How accurately can Z^* be measured?
2. With what precision can Z^* be measured?

(B) Clinical.

3. Can an accurate measurement of Z^* to the precision currently attainable detect the small chemical changes which may accompany disease?
4. Will a measurement of Z^* affect clinical management?

1. *Accuracy*

Accurate measurements at two distinct energies of μ, the linear attenuation coefficient of the material under investigation, should produce accurate measurements of Z^*. It is essential, therefore, that an accurate correction for the fact that the X-ray beam is polychromatic can be made (McCullough *et al.*, 1974; Brooks and Di Chiro, 1976). Such a correction appears to have been implemented in the EMI brain scanner programme (Rutherford *et al.*, 1976a and b).

Information needed to calculate Z^* is to be derived from the change in attenuation values when X-ray beam energy is changed from 100 kV to 140 kV. This difference is small. The measurement of Z^* is therefore extremely sensitive to errors in the measurement of μ. Such errors may arise due to (a) artefacts, (b) patient movement, (c) patient position in sequential scans, (d) position of material within the depth of a CT section.

2. *Precision*

It has already been shown that if the 100 kV and 140 kV beams are employed, Z^* may be measured to a precision of about 3% (± 0.2) for a 25 element region, or 1.5% (± 0.1) for a 100 element region (Rutherford *et al.*, 1976b).

Precision can be improved by employing beam energies that are further apart. Measurement of Z^* to 0.25% (± 0.02) for a 25 element region may be achieved by use of beam energies of 40 keV and 80 keV provided that an accurate correction for the polychromaticity of the beam can be made at these energies (Rutherford *et al.*, 1976c).

3. *Chemical change in disease*

It is important to recognize that electron density and effective atomic number, Z^*, are measures of mean composition of material. This is so whether the material is contained within one or 25 elements.

A number of factors may influence the effective atomic number, Z^*. The effect of different concentrations of various atoms on Z^* has been modelled. The assumption has been made that atoms are added to water and that the concentration of water molecules remains unchanged (Fig. 1). The concentrations of those atoms which might be detected if Z^* could be measured to a precision of ± 0.1 are considered in Table I. It is clear that concentrations of atoms below the limits considered would not produce a measurable change in Z^*.

Higher atomic number materials, as might be expected, are more readily detectable. It is known that the administration of iodine to the vascular system will raise the average attenuation level of blood at 120 kV by 12–15 Hounsfield units per 1 mg/ml increase in iodine concentration (Riding

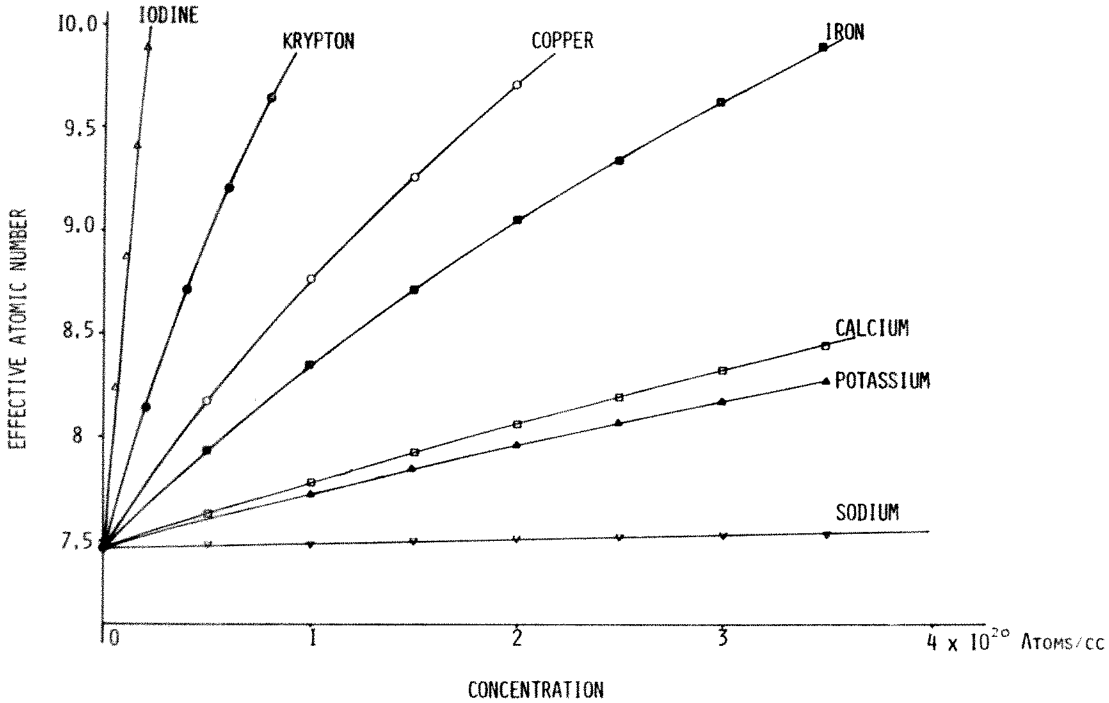


Fig. 1.

Effect of different concentrations of various atoms on effective atomic number Z^*.

TABLE I

THE LIMITS OF DETECTION IF Z^* CAN BE MEASURED TO ± 0.1

Element	Concentration, mg/ml
Sodium	19.9
Potassium	2.6
Calcium	2.0
Iron	0.93
Copper	0.69
Krypton	0.42
Iodine	0.11

et al., 1975). If a change in Z^* is due solely to the presence of iodine or other high atomic number element it should be possible to estimate the amount of such an element in tissue with accuracy and precision. This is not usually the case—both normal and pathological tissue contain a variety of elements, many of which are of low atomic number. The mean Z^* will be affected by the relative proportions of high and low atomic number elements. Subtle changes may therefore be difficult to detect.

4. *Clinical management*

There is no doubt that CT scanning of the brain has significantly affected clinical management by visual demonstration of density differences to be found in normal brain and pathological processes which affect it.

The role of electron density and Z^* measurement in clinical management will need, therefore, to be in the improvement of detectability of disease, the more accurate differentiation of disease processes or the study of biological pathways.

Part II: Colloid cysts of the third ventricle

Colloid cysts comprise 0.55% of all intracranial tumours (Poppen *et al.*, 1953). Diagnosis by clinical and traditional neuroradiological methods may be

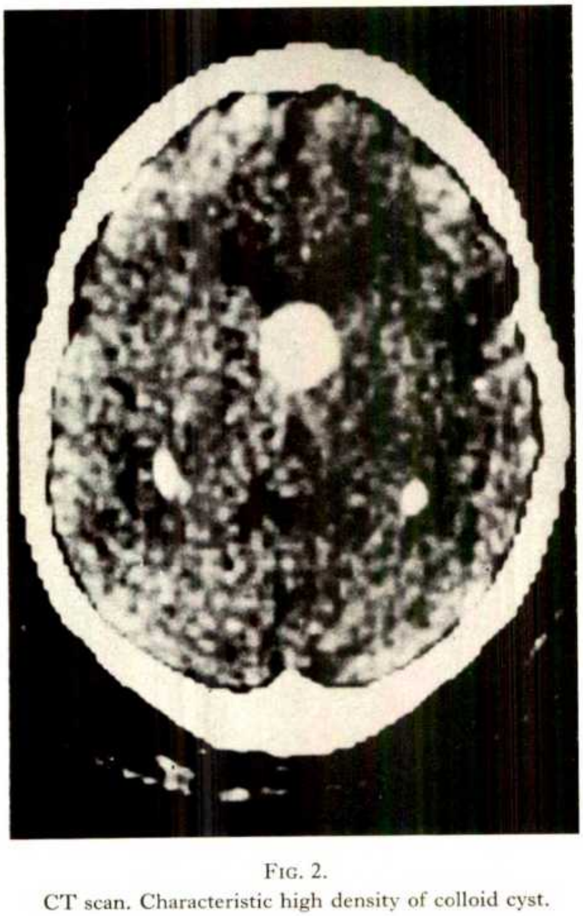


FIG. 2.

CT scan. Characteristic high density of colloid cyst.

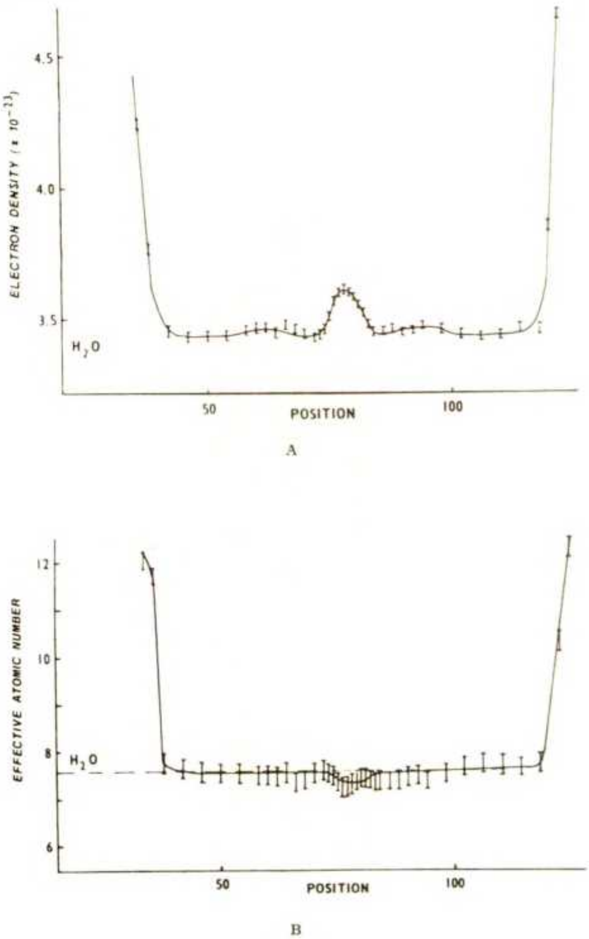


FIG. 3.

(A) Electron density and (B) effective atomic number as functions of position across a colloid cyst.

difficult. A recent series described by Sage *et al.* (1975) contained 38 cases in most of whom the diagnosis was made by conventional neuroradiological methods. In this series the most useful investigation was air encephalography.

The value of computed tomography in the diagnosis of colloid cysts has been appreciated more recently (Rutherford *et al.*, 1976b; Isherwood *et al.*, 1975; Sackett *et al.*, 1975).

Colloid cysts of the third ventricle have a characteristic high density (Fig. 2). The high attenuation value has been shown to be due to an increased electron density rather than to any contribution from high atomic number elements (Rutherford *et al.*, 1976b) (Fig. 3).

TABLE II

COLLOID CYSTS. TWENTY-THREE PATIENTS 1940–76. THREE DIED BEFORE TREATMENT

Treatment	Number	Died
Ventriculo-cisternostomy only		
—Bilateral	14	1
—Unilateral	1	1
Surgical removal	3	1
Ventriculo-cisternostomy and removal	2	0

Survivors of by-pass group = 13 (86%).

MATERIAL AND METHOD

Twenty-three patients with colloid cysts have been investigated and treated in the Departments of Neuroradiology and Neurological Surgery of Manchester Royal Infirmary over the years 1940 to 1976. These patients are the subject of a separate clinical review (Strang and Isherwood, 1977).

Fifteen patients (65%) were treated solely by bilateral Torkildsen's ventriculo-cisternostomies. Thirteen, *i.e.* 86% of this group, are alive and well (Table II). Of these survivors, 12 have been located and recalled for double-energy computed tomographic scanning. In nine of these patients, it was possible to calculate the electron density and effective atomic number of the colloid cyst. Movement between successive scans made such calculation impracticable in two patients.

One patient (C.L.), who died before treatment, was also diagnosed by CT scan. The colloid cyst subsequently removed at post-mortem was rescanned at two beam energies and was also the subject of histological and chemical analysis.

RESULTS AND DISCUSSION

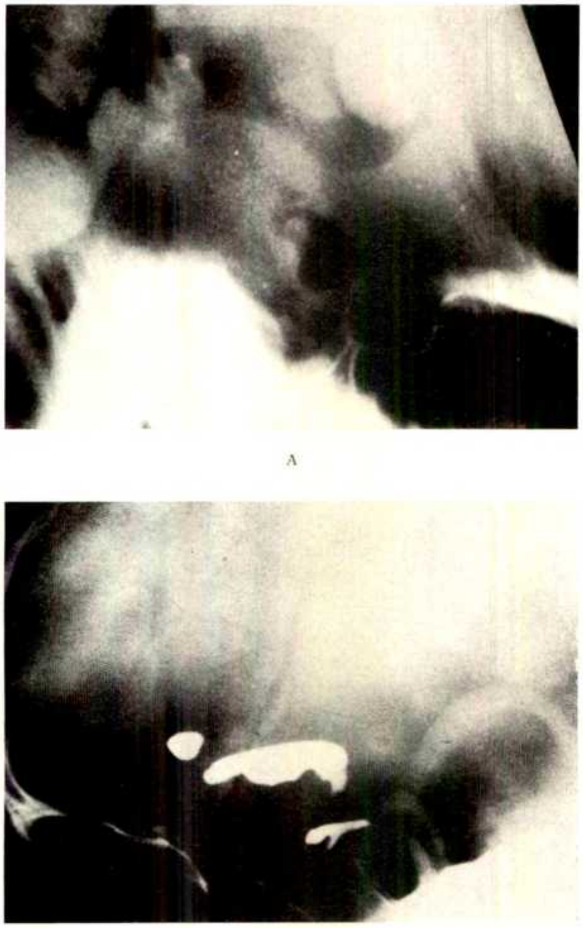
The clinical details of the 12 surviving patients with ventriculo-cisternostomies and of the one

TABLE III

DETAILS OF PATIENTS WITH VENTRICULO-CISTERNOSTOMIES

Patient	Age (1976)	Sex	Duration of symptoms, pre-op (Years)	Post-op survival (Years)	Definitive radiological procedure
J.K.	55	M	2	23	MV
J.H.	53	M	5	22	MV
A.B.	62	F	3	20	AV
P.G.	56	M	10 days	17	MV
H.D.	71	F	0.5	12	MV
P.K.	40	M	1.5	8	MV
J.E.	57	M	0.25	7	AEG
S.H.	34	F	3	4	MV
R.H.	55	F	0.25	4	MV
V.S.	47	F	15	2	CT
G.L.	53	M	2	2	CT
C.C.	23	M	0.5	1	CT
*C.L.	32	M	0.6	—	CT

MV = Myodil Ventriculogram; AV = Air Ventriculogram; AEG = Air Encephalogram; CT = Computed Tomography.
* Excised specimen.



A

B

FIG. 4.

Colloid cysts demonstrated by (A) Air Encephalogram—sagittal tomogram; (B) Myodil Ventriculogram.

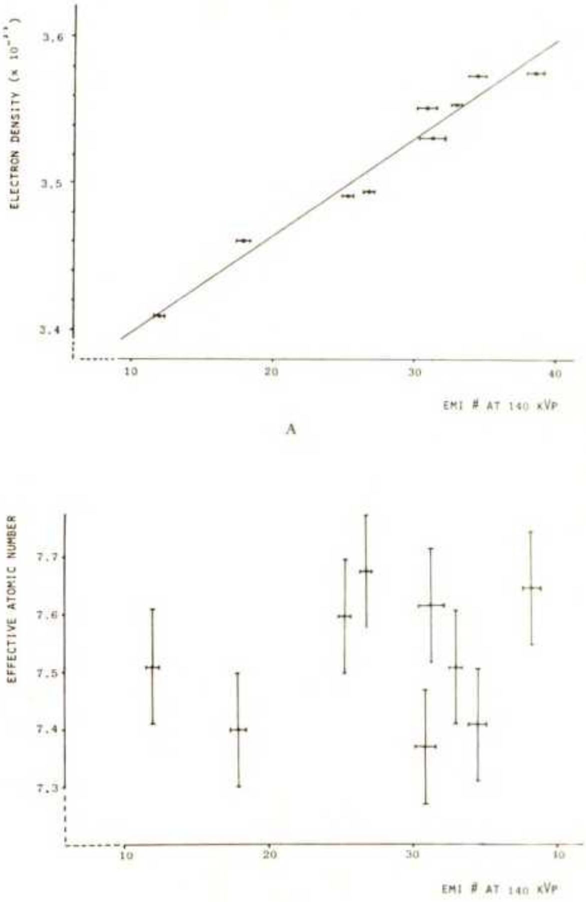


FIG. 5.

(A) Electron density and (B) effective atomic number of 12 colloid cysts expressed as functions of attenuation value at 140 kV.

TABLE IV

ANALYSIS OF CYSTS BY COMPUTED TOMOGRAPHY

Patient	Size (Pixels 1.5×1.5 mm)	EMI #100 kV mean ± S.E.	EMI #140 kV mean ± S.E.	Mean electron density $(\pm 0.01) \times 10^{23}$ electrons /c.c.	Mean effective atomic number (Z*) (±0.1)
J.K.	44	19.7 ± 0.6	17.9 ± 0.5	3.461	7.40
J.H.	62	31.0 ± 0.4	26.8 ± 0.4	3.495	7.68
A.B.	146	43.3 ± 0.7	38.3 ± 0.6	3.577	7.65
P.G.	38	35.5 ± 1.0	31.3 ± 0.9	3.532	7.62
H.D.	44	23.0 ± 0.6	26.3 ± 0.6	Movement	—
P.K.	164	36.3 ± 0.5	33.0 ± 0.4	3.555	7.51
J.E.	42	13.5 ± 0.4	12.0 ± 0.4	3.409	7.51
S.H.	38	32.8 ± 0.8	30.9 ± 0.7	3.553	7.37
V.S.	135	37.0 ± 0.6	34.5 ± 0.6	3.575	7.41
G.L.	77	32.8 ± 0.9	28.6 ± 0.7	Movement	—
C.C.	76	28.7 ± 0.6	25.3 ± 0.4	3.492	7.60
*C.L.	60	21.2 ± 0.6	17.8 ± 0.5	3.433	7.67

* Excised specimen

patient who died before treatment are contained in Table III.

Eight patients were male and the age range at the time of operation was from 22 to 59 years (mean 40.4 years).

Post-operative survival periods ranged from one to 23 years which with an added estimation of duration of symptoms indicated a possible tumour age of up to 27 years.

TABLE V

CHEMICAL ANALYSIS OF EXCISED COLLOID CYST

Water	88.7%
Carbon	5.6%
Nitrogen	1.41%
Hydrogen	0.78%
Sodium Chlorine Potassium Oxygen	3–4%
Iodine	Nil
Calcium	Nil

The definitive diagnostic radiological procedure in the present group of patients was myodil ventriculography in seven, air ventriculography in one, air encephalography in one and computed tomography in four (Fig. 4).

Results indicating estimated size in pixels and attenuation values at two energies together with electron density and effective atomic number estimations for colloid cysts in nine survivors and one specimen tumour are recorded in Table IV.

Size does not appear to have any relation to estimated age of tumour. An attempt was made to calculate size from the original conventional neuroradiological investigations but this proved to be unreliable. Subjective impressions do not suggest any significant change in size or shape in any individual tumour from initial diagnosis to current CT scan.

Attenuation values of colloid cysts in 11 patients and one post-mortem specimen range from 13.5 to

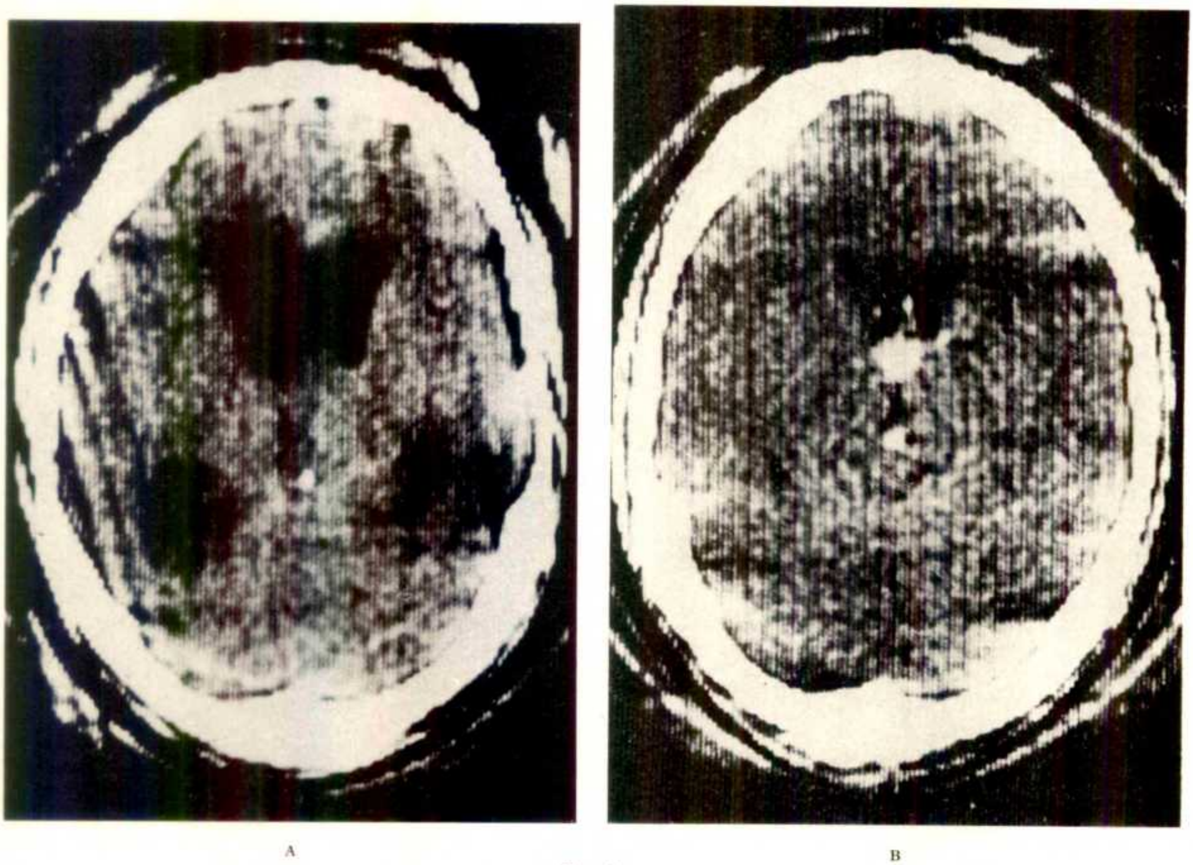

A B

FIG. 6.

CT scan (C.C.). (A) Before and (B) after ventricular drainage.

43.3 (mean 29.56) at 100 kV and 12.0 to 38.3 (mean 26.89) at 140 kV.

Electron density of 12 colloid cysts expressed as a function of attenuation value at 140 kV demonstrates a consistent relationship. Effective atomic number, however, has no such relationship (Fig. 5).

Chemical analysis of the excised colloid cyst specimen is given in Table V. There was no evidence of high atomic number material within the cyst. Histological analysis confirmed the nature of the lesion.

The colloid cyst of one patient (C.C.) was not detected at the initial CT examination. Dilatation of the ventricular system was noted. The lesion was readily identified two weeks after bilateral Torkildsen's ventriculo-cisternostomy (Fig. 6). The explanation for this phenomenon is almost certainly that the initial sections were not sufficiently low to include the tumour. The colloid cyst may itself have been displaced inferiorly by the dilated lateral ventricles. It is important to emphasize, therefore, that sections must include the suprasellar structures; where clinical suspicion of a colloid cyst exists with associated hydrocephalus, a repeat scan following ventricular drainage may be of value.

The long-term survival of patients treated solely by bilateral Torkildsen's ventriculo-cisternostomies together with the evidence that colloid cysts do not change in size or chemical character over long periods suggests that this simple surgical approach to the problem is safe and effective (Strang and Isherwood, in preparation).

ACKNOWLEDGMENTS

The authors wish to thank Miss H. Jarvis and the radiographic staff of the Department of Neuroradiology for their support. Thanks are also due to Mrs. G. E. H. Shawcross for the preparation of illustrative material and to Mrs. M. Tipton for her helpful secretarial assistance.

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Book review

Pocket Atlas of Skeletal Age. By T. de Roo and H. J. Schroder, pp. 130, illus., 1976 (The Netherlands, Martinus Nijhoff), Dfl.36.

As indicated by the title, this is a small atlas of radiographs for the rapid assessment of skeletal age. It has been felt necessary to begin with an illustration of a mature hand in which the bones are annotated and accompanied by a legend of names. There follow 31 illustrations of the development of the male hand with a second section containing 27 similar illustrations of the female hand. Each illustration is accompanied by a succinct description of the salient features. Readers familiar with a certain larger atlas of bone age will find much of the descriptions to be of familiar phraseology. The illustrations are printed against a black background and are of high contrast.

In the three short paragraphs of the introduction the standard reference books are dismissed as difficult to use and useless for quick interpretation with illustrations which are often not clear. This new book will be appreciated by those radiologists who sympathize with these criticisms. It will satisfy radiologists who wish to assess bone age on the basis of simple pictorial comparison and desire a small inexpensive source of standard radiographs.

J. ROYLANCE.

1977, *British Journal of Radiology*, *50*, 620–625

Mixed connective tissue disease—clinical and radiological aspects of 20 cases

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ABSTRACT

The clinical and radiological features of 20 cases of mixed connective tissue disease (MCTD), a newly defined disorder, are described. MCTD shares a number of abnormalities with other collagen diseases, notably diffuse systemic sclerosis and systemic lupus erythematosus. However, patients with MCTD have a specific circulating antibody to extractable nuclear antigen (ENA). Most of the cases described exhibited multi-system involvement with radiological changes in the skeleton, chest, and gastro-intestinal tract. Twelve of the 20 cases had an erosive arthritis. This finding has not been previously noted in the radiological literature.

Mixed connective tissue disease (MCTD) is a newly recognized disorder, recently defined by Sharp and colleagues (Sharp *et al.*, 1972). The disease shares a number of clinical and radiological features with systemic lupus erythematosus (SLE), polymyositis, and diffuse systemic sclerosis (DSS), but can be separated from these entities by demonstrating the presence of high titres of antibodies to RNA-ase-sensitive extractable nuclear antigen (ENA). Since its first description, there have been several communications describing the various clinical aspects of the condition (Sharp, 1975a, 1975b; Northway and Tan, 1972; Reichlin, 1976). The radiological literature, however, is limited to one report of three cases (Silver *et al.*, 1976). Although the radiological features of MCTD are diverse, the presence of "overlap" radiological features of SLE, DSS, and polymyositis may enable the radiologist first to suggest the diagnosis. Original reports have emphasized the rarity of bone erosion (Sharp, 1975a; Northway and Tan, 1972). We believe that the presence of asymmetrically distributed, small, punched-out bone erosions in a disease with clinical and radiological features of an overlap syndrome is suggestive of MCTD. These erosions were present in 12 of our 20 cases.

We wish to report the clinical and radiological features of 20 patients with this interesting, new disease.

PATIENTS AND METHODS

Over the course of the past four years 20 patients with MCTD have been followed by one of us (R.M.B.). The basis for this diagnosis was the presence of a clinical overlap syndrome, a high titre of a speckled pattern anti-nuclear immunofluorescence, negative Sm antibodies, negative double-stranded DNA antibodies, and a high titre of antibodies to RNA-ase-sensitive ENA. These features define MCTD, as recently outlined by Sharp *et al.* (1976).

Antibodies to ENA were assayed by a modification of Sharp's haemagglutination assay (Sharp *et al.*, 1972) as previously described (Bennett and Spargo, 1977). RNA-ase-sensitivity was taken as a fall in the haemagglutination titre to 1:1000 or less after RNA-ase digestion; a high titre without RNA-ase-sensitivity was indicative of Sm antibodies.

Antibodies to double-stranded DNA were measured by a modification of the Farr technique (Bennett and Molina, 1976), using DNA, which had been characterized as double stranded, by benzoyolated naphthoylated DEAE cellulose chromatography (Locker *et al.*, 1977).

Fine detail radiographs of bones and joints employed industrial film, as outlined by Genant *et al.* (1976).

CLINICAL FEATURES

The clinical picture at the time of presentation was varied. These were the initial diagnoses of the 20 patients found to have MCTD: DSS in two, SLE in five, discoid lupus in one, juvenile rheumatoid arthritis in one, sero negative rheumatoid arthritis in nine, psoriatic arthropathy in one, and erythema nodosum in one.

Over the course of follow-up, the clinical findings fluctuated in an unpredictable manner with "overlap" symptoms being a conspicuous feature. Of the nine patients presenting with a rheumatoid arthritis-like picture, five progressed to sclerodermatous changes. Ten patients had CNS involvement, the commonest problem being an aseptic meningitis. Four patients underwent a renal biopsy, and all had an immune complex nephropathy with membranous changes in light microscopy (Bennett and Spargo, 1977). The patient with clinical and radiographic features of psoriatic arthropathy had the changes of discoid lupus on skin biopsy, and one patient presented with discoid lupus. Six out of nine patients had abnormal pulmonary function tests with a reduced diffusing capacity. Eight out of 18 had abnormal oesophageal motility, demonstrated either radiologically or by manometry. Another eight patients had evidence of an inflammatory myositis during the course of their disease, whilst an intermittent fever was a major symptom in nine patients. Most patients have done well, usually being controlled by a small amount of prednisone. Four patients have died, one from post-operative pulmonary embolism, two from fulminant respiratory failure, and one from pulmonary arterial hypertension.

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Radiological Features

1. *Musculo-skeletal*

As MCTD is a multi-system, collagen-vascular disease, there was a wide variety of radiological features in the 20 cases. The commonest abnormality was the presence of peri-articular cortical erosions in the small bones of the hands and feet. The erosions were small and had a punched-out appearance, being most commonly found in the phalanges (Fig. 1). The erosions were usually asymmetrically distributed. These were present in 12 of the 20 cases and, as such, were the most frequent radiological abnormality.

In two of these 12 cases the only abnormality was a single erosion in the base of a phalanx (Fig. 2) or in the styloid process of the ulna (Fig. 3). Extensive erosive changes in all the bones of the hands

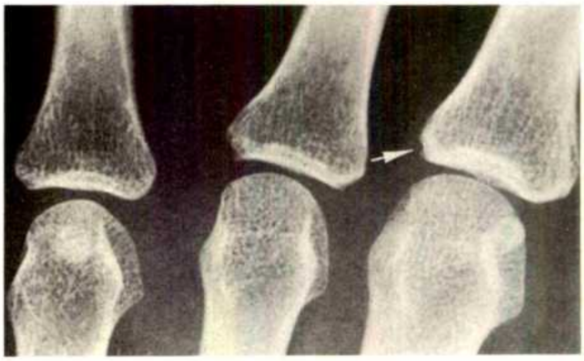


Fig. 2.

There is a small erosion (arrowed) at the base of a proximal phalanx.

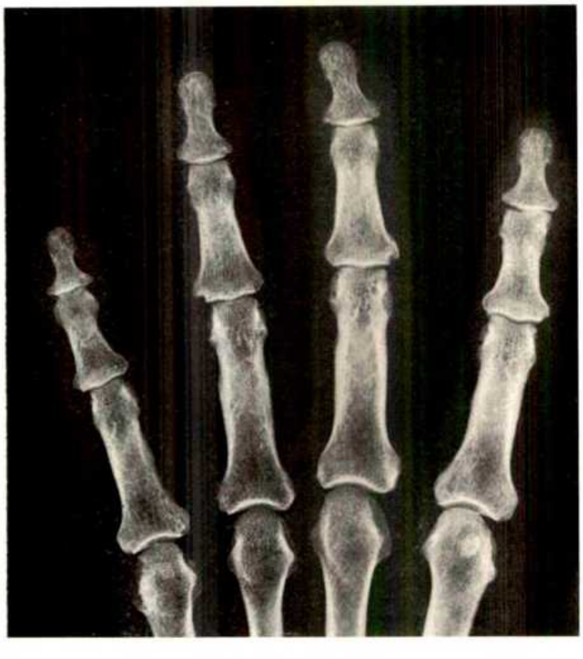


Fig. 1.

There are small erosions in the proximal interphalangeal joints.

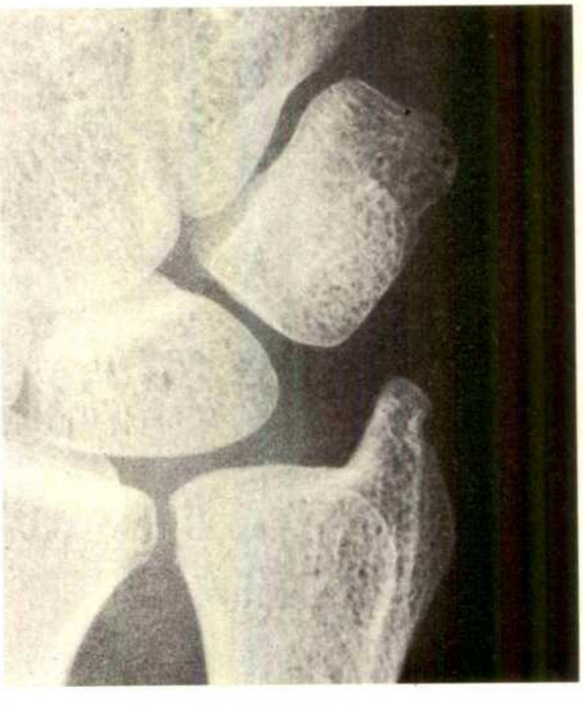


Fig. 3.

A small cortical erosion is present in the styloid process of the ulna.

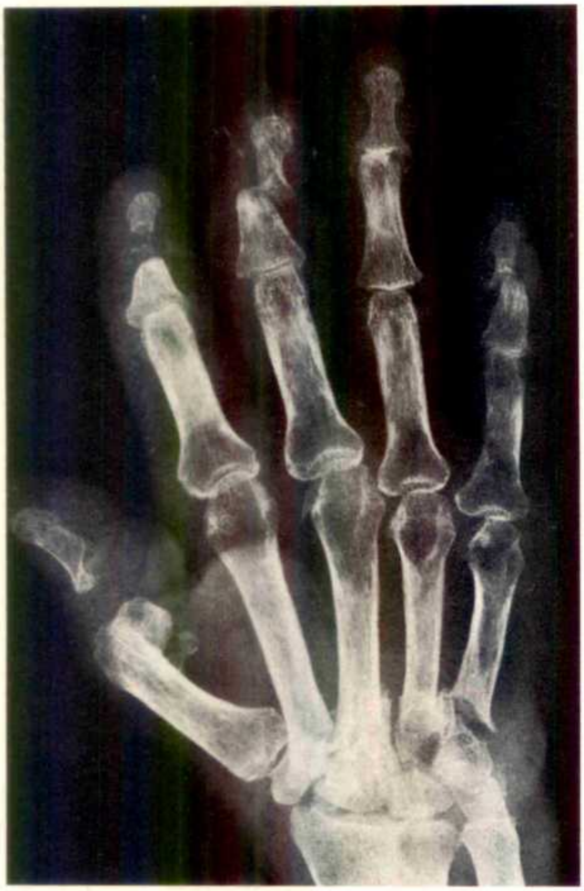


FIG. 4.

Extensive erosive changes are present in the carpus and small joints of the fingers, with associated loss of bone density.

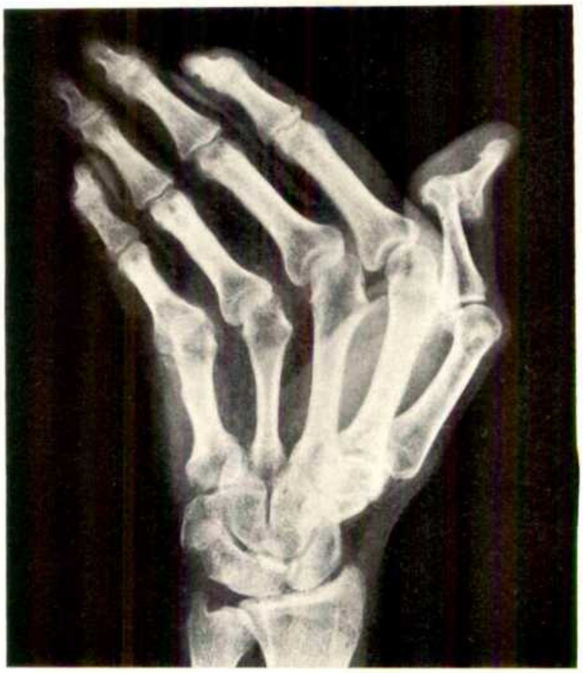


FIG. 5.

There are multiple subluxations at the metacarpo-phalangeal joints with dislocation at the DIP joint of the thumb.

and wrists, resembling those seen in psoriatic arthritis, were present in two cases (Fig. 4). Two other patients had diffuse peri-articular loss of bone density and subluxations of the metacarpo-phalangeal joints (Fig. 5), both features frequently found in SLE (Noonan *et al.*, 1963). In three cases, there were additional erosions of the tufts of the distal phalanx, usually associated with local soft tissue loss (Gondos, 1960). There were no bony changes in two of the 20 cases.

Atrophy of the pulp of one or several fingers was present in six patients. This was associated with acro-osteolysis in three. Peri-articular soft tissue calcification was the only abnormality in one case (Fig. 6). This patient had presented with Raynaud's phenomenon, seizures, and arthritis. Three patients exhibited avascular necrosis of bone. One of these developed changes of avascular necrosis in a hip (Fig. 7), although she was taking only 10 mg of prednisone per day. Avascular necrosis of both scaphoid bones was evident in another, and in a third patient there was bilateral avascular necrosis of the navicular bones. Another patient had a mottled density in the humeral diaphysis, consistent with a bone infarct.

2. *Cardio-pulmonary*

The chest radiograph was abnormal in seven cases. Three of these had reticulo-nodular shadowing at the lung bases, indicating interstitial fibrosis (Fig. 8). One patient had no abnormal pulmonary shadowing but was consistently unable fully to expand the lungs—presumably due to diminished lung compliance. This abnormality has been previously described in patients with SLE (Hoffbrand and Beck, 1965; Matthay *et al.*, 1974).

Another patient had shrinkage of both lower zones with band-like opacities consistent with subsegmental collapse-consolidation. These features were thought to be caused by an inflammatory pneumonitis because there was a rapid response to steroids (Matthay *et al.*, 1974; Bulgrin *et al.*, 1960). Increasing effort dyspnea was a major complaint of another patient whose chest radiograph showed

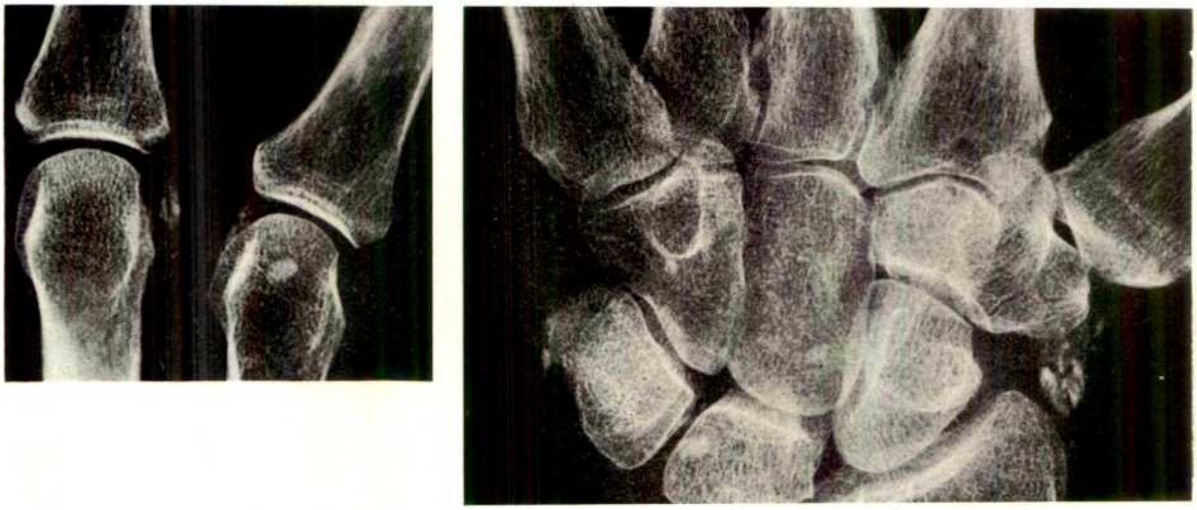
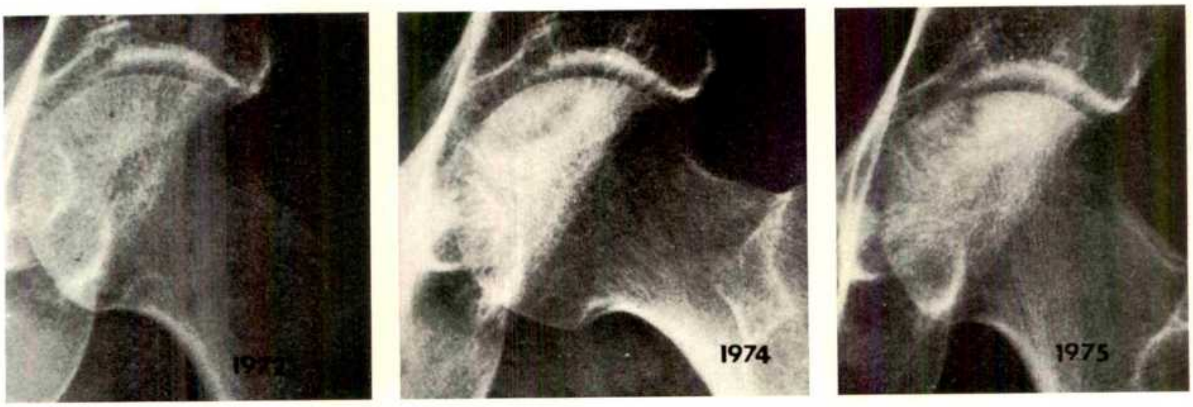


FIG. 6.

There is a peri-articular calcification in the carpus and at several MCP joints.



A B C

FIG. 7.

Progressive avascular necrosis of the left hip is present.

slight cardiomegaly. The pulmonary trunk was dilated, but the peripheral vessels in the left upper zone were narrow and attenuated (Fig. 9). A lung scan showed multiple perfusion defects particularly in the left upper lobe, consistent with the presence of pulmonary emboli. This patient died of progressive pulmonary arterial hypertension and at autopsy was found to have a diffuse pulmonary arteritis with multiple arterial occlusions. Thus, in one patient, MCTD was associated with progressive pulmonary arterial hypertension, which has not been described previously.

None of the patients had pleural effusions, but one developed an acute pericardial effusion, which was confirmed by a radionuclide scan.

3. *Gastro-intestinal*

The gastro-intestinal manifestations of MCTD in this series were variable. Of the four patients who had colon examinations, all had classical pseudo-diverticula on the anti-mesenteric border (Fig. 10). One of these patients had pneumatosis cystoides intestinalis of the small bowel in addition (Fig. 11). This had not been previously described as a complication of MCTD, although it is known to occur in DSS and SLE (Nelson, 1972). A barium meal and

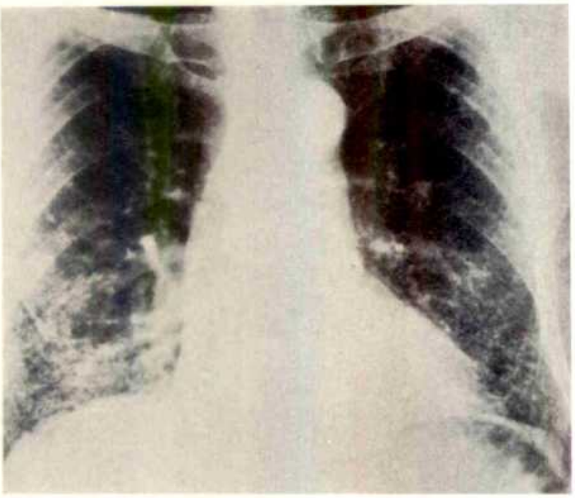


Fig. 8.
There is interstitial fibrosis at the lung bases.

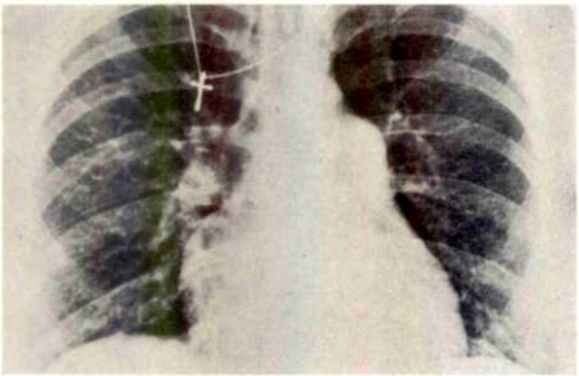


Fig. 9.
There is moderate cardiomegaly. The pulmonary trunk is dilated and there is a paucity of vessels in the left upper zone.

follow-through examination was performed in five patients, three showing an atonic, dilated oesophagus with lower oesophageal stricture in one (Tatelman and Keech, 1966). Only one of the five patients whose small bowel was examined showed evidence of small bowel dilatation.

4. *Miscellaneous*

Because of recurrent parotitis, sialography was performed on two patients. Both examinations showed atrophy of the normal glandular tissue with loss of the normal duct branches and diffuse punctate sialectasis—features compatible with Sjögren's syndrome.

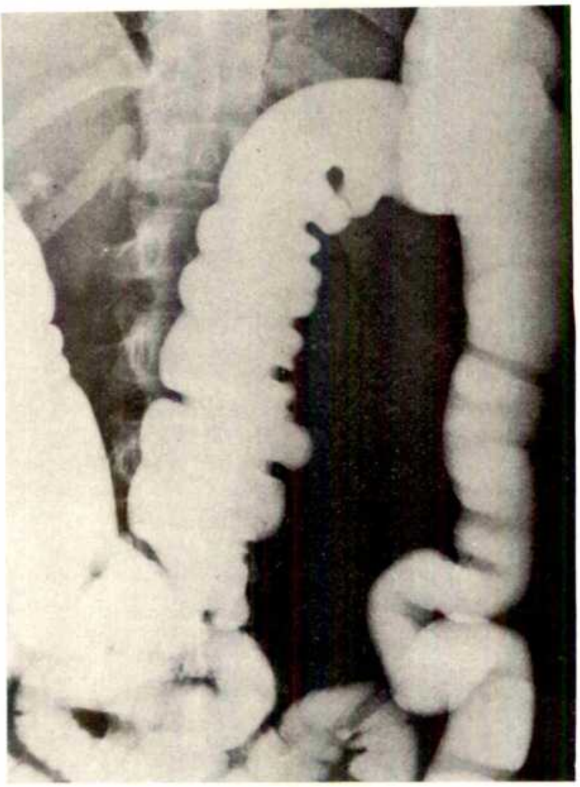


Fig. 10.
There are wide-mouthed diverticula on the anti-mesenteric side of the transverse colon.

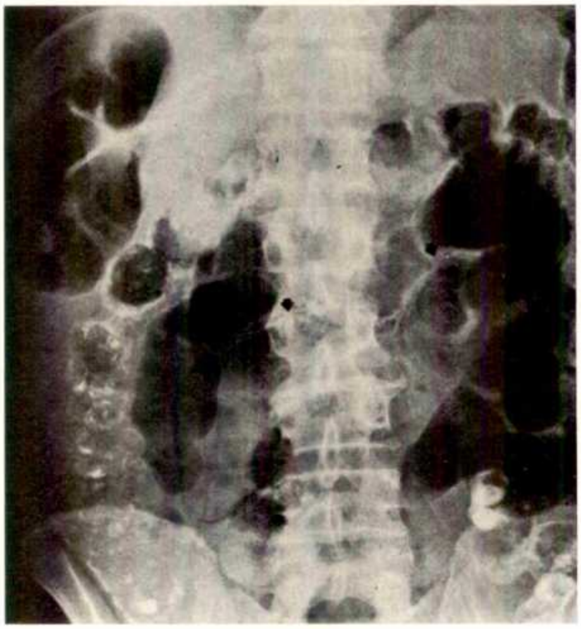


Fig. 11.
There is a linear collection of intra-mural air in the wall of the small intestine (arrowed). Residual barium is present in the colon.

Discussion

The protean clinical and radiological manifestations of MCTD are evident in the 20 cases described above. There are many clinical and radiological features present in MCTD which were previously thought exclusive to diffuse systemic sclerosis (DSS) and SLE. The presence of overlap features, however, should alert one to the possibility of MCTD. The index of suspicion should be high if there are minor erosive changes in the small bones of the hands or feet. Cortical erosions are rare in DSS and SLE (Noonan *et al.*, 1963; Rodnan and Medsger, 1968), but were found in 12 of the 20 cases of MCTD described here. The erosions may be few in number and are more easily appreciated on fine detail films of the hands and feet (Genant *et al.*, 1976).

The presence of cortical erosions in a syndrome with clinical and radiological features which do not conform to the classical features of DSS and SLE should suggest the diagnosis of mixed connective tissue disease. This can be further substantiated by appropriate serological studies.

Acknowledgment

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The oblique view at mammography

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ABSTRACT

On review of 392 cases of mammary carcinoma it was found that 27 cases were visible in the oblique view only at mammography. It would seem reasonable to include this view in a standard diagnostic mammography.

Most radiologists take only two views of each breast at mammography, one cranio-caudal and one lateral. Since starting mammography in 1969 I have also used an oblique view, which almost without exception seemed to give an image of the breast covering more area, depicting more of the glandular tissues and being easier to read than the other two (Lundgren, 1976).

This is based on anatomical factors: with the arm raised the breast can be seen as a continuation of the pectoral muscle in a caudal-medial direction. It is easy to position the patient provided the examination table and the film are placed with one end under the upper part of the pectoral muscle (Fig. 3).

It is also natural that this view gives more information, since in the oblique view the X-ray beam has a shorter course through denser tissues compared with the other two views (Fig. 1). This gives better contrast and lessens the probability of lesions being hidden in tissue of more or less equal density. Finally, this view includes the tail of the glandular tissues of the breast, which can seldom be visualized in a cranio-caudal view, and not often in a lateral (Fig. 2).

It would seem, therefore, that the oblique view should be the most informative one of the three. The aim of this study was to establish if more carcinomas could be detected or excluded by using the oblique view alone or in combination with the other two views.

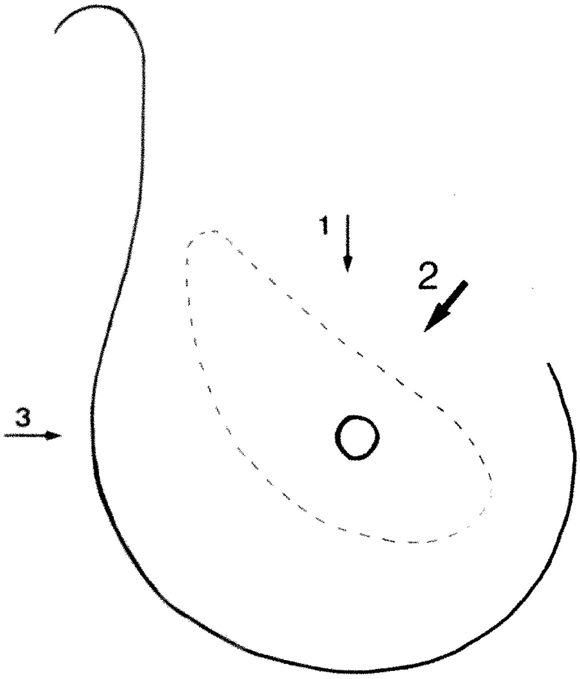

FIG. 1.

Beam directions in the standard views at mammography. Interrupted line represents normal localization of the glandular tissues of the breast.

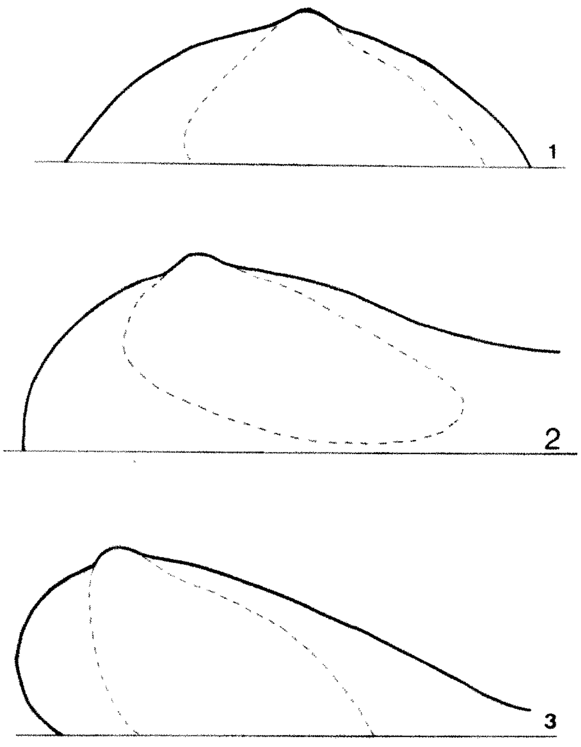

FIG. 2.

Normal visibility of the glandular tissues, represented by interrupted lines, in the three standard views at mammography.

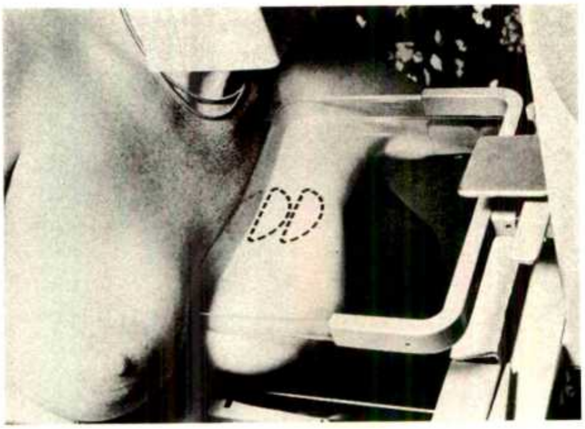

FIG. 3.
Positioning of oblique view.

TABLE I

AGE DISTRIBUTION OF 392 CASES OF MAMMARY CARCINOMA, EXAMINED BY THREE-VIEW MAMMOGRAPHY

Age	Number	%
–29	1	(0.2)
30–39	8	2
40–49	62	16
50–59	96	24
60–69	118	30
70–	107	27
	392	100

MATERIALS AND METHOD

A total of 397 consecutive cases of histologically verified mammary carcinoma were reviewed. In five cases it was discovered that one of the three views had been lost or not been done. The remaining 392 cases were analysed. The age distribution of the patients appears in Table I.

Of the 392 cases, 352 had been examined clinically at the Department of Oncology, Gävle Hospital, the remainder by a senior surgeon at Sandviken Hospital. It was not possible to detect 107 of the 392 cases (27%) on clinical examination. These were detected by mammography alone. On the other hand 22 cases were detected by clinical examination only (6%). In this material 185 cases were detected in several population screening programs, and the remaining 207 at the Department of Oncology, which is a referral clinic. Parts of this material has been used in another study (Lundgren, 1977).

The three original standard mammography views of each case were reviewed and it was decided in which views the carcinomas were visible wholly, partly, or not at all.

TABLE II

CASES OF MAMMARY CARCINOMA VISIBLE IN ONLY ONE OR TWO VIEWS AT MAMMOGRAPHY

	Number
One view only	
Cranio-Caudal	1
Lateral	1
Oblique	27
Two views	
Cranio-Caudal/Oblique	29
Lateral/Oblique	27
Cranio-Caudal/Lateral	0
Total	85

TABLE III

FOUR CASES OF MAMMARY CARCINOMA INCORRECTLY REPORTED AS NEGATIVE AT ORIGINAL MAMMOGRAPHY AND THE VIEWS IN WHICH THEY WERE VISIBLE ON REVIEW

View	Case 1	Case 2	Case 3	Case 4
Cranio-Caudal	1	1	1	0
Oblique	1	1	1	1
Lateral	0	0	1	0

TABLE IV

VISIBILITY OF 392 TUMOURS IN THE THREE STANDARD VIEWS

View	Tumours visible Number	%
Cranio-Caudal	319	81
Oblique	372	95
Lateral	315	80

RESULTS

In 289 of the 392 cases (74%) the tumours were visible in all three views. In 85 cases (22%) the tumour was visible in one or two views only. In all but two of these 85 cases the tumour was visible in the oblique view alone or combined with one of the other two views (Table II). The cranio-caudal and the lateral views were the sole indicators of cancer in one case each, whereas the oblique view alone showed the lesion in 27 cases, or 7% of the total material.

In this material 22 cases (6%) were originally reported as negative at mammography. In 18 of these (4%) none of the three views showed signs of tumour on review. In the remaining four signs of malignancy were visible, but had been incorrectly interpreted (Table III). All were visible in the oblique view, three in the cranio-caudal and one in the lateral.

Thus 26 of the 27 cases visible in the oblique view only were originally interpreted correctly.

Eighty-one per cent of the tumours were visible in the cranio-caudal view, 80% in the lateral and 95% in the oblique view (Table IV). Only two of the 20 cases not visible in the oblique view could be detected in the other two—one in the cranio-caudal and one in the lateral (Table II).

Discussion

If the oblique view had not been used in these patients 26 cases would have been added to the 22 false negatives, increasing this rate from 6% to 12%. Furthermore 16 of these 26, with an average size of 6 mm, were not detectable at clinical examination. Had the oblique view not been used, the mammographic diagnosis in another 56 cases would have rested solely on the evidence of either a cranio-caudal (28 cases) or lateral view (28 cases). It is the author's opinion that the correct diagnosis would have been difficult to reach in some of these cases.

The oblique view should always be included at diagnostic mammography since it appears to be the most informative one in the diagnosis of mammary carcinoma. It follows that it also supplies additional information, thereby helping to exclude carcinoma.

No attempt has been made to evaluate whether all the 368 cases visible in the oblique view and originally correctly diagnosed also would have been detected by using this view only. In fact 61 of these cases were detected that way in the course of population screenings.

The considerations behind this study have been the basis for the introduction of population screening for mammary carcinoma by the single-view mammography approach, where the oblique view only is used for screening. At the time of writing more than 40000 women have been screened by this method (Lundgren and Jakobsson, 1976).

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Book review

Early Breast Cancer—Its history and results of treatment. By Carl M. Mansfield. Experimental Biology and Medicine, No. 5, pp. vi+129 (Switzerland, S. Karger), $19.00

This concise paperback is a valuable review of the present knowledge of the management of early breast cancer. It reviews the past and present results of treatment including current clinical trials.

The opening historical review of the earliest references to the disease, followed by comments from the many well-known figures of the 19th and early 20th centuries, is of considerable interest. Sir James Paget, Charles Moore, and W. S. Halsted are amongst these followed by the views of the less radical school including D. H. Patey and others. There is a useful reminder of the exact nature of the various operations, for those who are not surgeons but who are involved in the management of this disease. The criteria of operability with classification and staging is included.

Current progress with various forms of surgery and details of many clinical trials for the early disease are discussed in a comprehensive way. Many of these were designed to evaluate radiation combined in various ways with surgery. There is also reference to the trials involving adjuvant chemotherapy which are now underway.

After careful consideration of the evidence, the author reached certain conclusions. In our present state of uncertainty over the management of this common cancer, it is useful to be reminded of the facts.

B. T. Hale.

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A computer assisted comparison of ^{99}Tc^{m}-methylene-diphosphonate and ^{99}Tc^{m}-pyrophosphate bone imaging

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ABSTRACT

A total of 350 patient studies were carried out using clinical trials' batches of the Technetium (MDP) agent for bone scintigraphy (The Radiochemical Centre), and a commercially available Technetium pyrophosphate agent (CIS). The bone seeking properties of ^{99}Tc^{m} Sn-methylene-diphosphonate (MDP) and ^{99}Tc^{m} Sn-pyrophosphate (PYP) were evaluated by their comparative uptake in compact bone, cancellous bone and soft tissue using a region-of-interest technique. From these data uptake ratios were computed in order to correlate the values with (a) the amount of ^{99}Tc^{m}-MDP injected, (b) the time after injection and (c) the age of patients examined. All ratios derived with ^{99}Tc^{m}-MDP were superior to those using ^{99}Tc^{m}-PYP and were not dependent on the amount of ^{99}Tc^{m}-MDP injected. Uptake ratios determined for ^{99}Tc^{m}-MDP (1.5 h to 2.5 h after injection) were found to be higher than those for ^{99}Tc^{m}-PYP 2.5 to 3.5 h after injection. Soft tissue accumulation of ^{99}Tc^{m}-MDP, visible on scintiphotos, occurred only in 26% of cases but with ^{99}Tc^{m}-PYP, in 75% out of all cases studied. A decrease of cancellous bone/compact bone ratios with increasing age of the patients was found with both radiopharmaceuticals. This is most probably correlated with a diminished mass and/or surface of the cancellous bone in the elderly patient.

Since their introduction by Subramanian and McAfee (1971), ^{99}Tc^{m}-labelled phosphates and phosphonates have predominated as agents for bone scanning. ^{99}Tc^{m}-Sn pyrophosphate (^{99}Tc^{m}-PYP) proved to have the best skeletal imaging properties of all labelled phosphate complexes (Ackerhalt *et al.*, 1974; Büll and Frey, 1973; Schümichen and Nakken, 1974; Subramanian *et al.*, 1975). ^{99}Tc^{m}-labelled methylene-diphosphonate (^{99}Tc^{m}-MDP) is superior to ^{99}Tc^{m}-labelled ethane-1-hydroxy-1, 1-diphosphonate (^{99}Tc^{m}-EHDP) (Subramanian *et al.*, 1975). Detailed data on biological kinetics, concentration in various tissues and target to non-target uptake ratios of both ^{99}Tc^{m}-PYP and ^{99}Tc^{m}-MDP have been obtained in animal studies (Subramanian *et al.*, 1975). In man, data on blood clearance and urinary excretion has been published, but less is known about uptake by cancellous bone, compact bone and soft tissues. Some authors (Citrin *et al.*, 1975; Snow and Weber, 1975) have published ratios of uptake in bony tumours to normal bone as well as to soft tissues, but no systematic evaluation of the quality of bone scans in terms of specific ratios has yet been made.

This study in 350 patients was undertaken as part of clinical trials of batches of the Technetium (MDP) bone agent (The Radiochemical Centre Ltd.) and a commercially available Technetium pyrophosphate agent (CIS). It was designed to measure cancellous to compact bone uptake ratios as well as of bone to soft tissues for both ^{99}Tc^{m}-MDP and ^{99}Tc^{m}-PYP and to compare these values with one another. Moreover, these ratios—all determined with the region-of-interest (ROI) technique—were correlated with the time after injection (1.5 h to 3.5 h) as well as with the patient's age (20 to 90 years) and the amount of ^{99}Tc^{m}-MDP (mg) injected.

PATIENTS

A total of 350 patients between 20 and 90 years of age were included in this study. Of these 227 (64.8%) had a normal bone scan. The remaining 123 patients showed a "pathologic pattern" of skeletal uptake. In the latter group X-ray examinations of 53 patients showed primary or secondary osseous tumours in the spine, pelvis or legs. Six patients were receiving long-term haemodialysis. The remaining 59 patients had patterns of focal increased or decreased skeletal uptake caused by metastases, osteoarthritis, fractures, etc., which were not localized to the areas mentioned above. These were added to the group of the 227 "normal" patients to form a group of 286 subjects used for comparison of ^{99}Tc^{m}-MDP ($n=140$) and ^{99}Tc^{m}-PYP ($n=146$) ratios.

MATERIALS

Supplies of Technetium (MDP) agent for bone scintigraphy were provided for clinical trial purposes by The Radiochemical Centre Ltd., Amersham. Pyrophosphate bone kits were purchased from CIS, Paris. The pertechnetate sources for the study were commercially available ^{99}Tc^{m} generators (Duphar, Petten, The Netherlands).

METHODS

A dose of 7.0 to 9.0 mCi of ^{99}Tc^{m}-MDP was injected, containing either 5.0 mg of MDP and

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TABLE I

Femur-to-soft tissue (F/ST), os sacrum-to-femur (S/F) and os sacrum-to-soft tissue (S/ST) ratios obtained 1.5 h to 2.5 h (A) or 2.5 h to 3·5 h (B) after injection of ^{99}Tc^{m} Sn-methylene-diphosphonate (MDP) in 140 patients classified into decades of age ((1) to (5)) with respect to amounts of MDP injected (1 vial = 5.0 mg of MDP; $\frac{1}{3}$ vial = 1.67 mg of MDP)

	^{99}Tc^{m}-MDP(Mean ± S.D.)							
	F/ST				S/F n = 72		S/ST	
A	n	$\frac{1}{3}$ vial p. pat.	n	1 vial p. pat.				
(1)	5	1.72 ± 0.34*	5	1.67 ± 0.18*	4.46 ± 0.82*	4.21 ± 0.62*	7.67 ± 1.72*	7.03 ± 1.84*
(2)	7	1.65 ± 0.35	6	1.83 ± 0.26*	3.22 ± 0.66	3.65 ± 1.04	5.31 ± 1.14	6.68 ± 1.67*
(3)	8	1.66 ± 0.26	7	1.63 ± 0.18	3.30 ± 0.95*	3.53 ± 0.32*	5.48 ± 1.73*	5.75 ± 0.95*
(4)	13	1.65 ± 0.28	11	1.58 ± 0.30	3.04 ± 0.54	3.19 ± 0.57*	5.02 ± 0.69*	5.04 ± 0.95*
(5)	5	1.57 ± 0.29*	5	1.45 ± 0.18	3.09 ± 0.76	2.65 ± 0.43	4.85 ± 0.62*	3.84 ± 0.77
B	n		n		n = 68			
(1)	7	1.80 ± 0.20*	5	1.70 ± 0.21	4.90 ± 0.84*	4.73 ± 0.64*	8.82 ± 1.35*	8.04 ± 2.03*
(2)	5	1.65 ± 0.17	5	1.60 ± 0.17	3.93 ± 0.65	3.23 ± 1.09	6.48 ± 0.62*	5.14 ± 1.49
(3)	8	1.59 ± 0.26	5	1.82 ± 0.41	3.33 ± 0.70*	3.09 ± 0.40	5.29 ± 1.42*	5.62 ± 1.30*
(4)	11	1.71 ± 0.32*	7	1.82 ± 0.23*	2.94 ± 0.73	3.24 ± 0.37*	5.03 ± 1.46*	5.90 ± 1.40*
(5)	10	1.78 ± 0.45	5	1.83 ± 0.28	2.99 ± 0.83	2.43 ± 0.49	5.32 ± 1.10*	4.45 ± 1.50

(1) 20–39 years of age
(2) 40–49
(3) 50–59
(4) 60–69
(5) >70
A 1.5 to 2.5 h after injection.
B 2.5 to 3.5 h after injection.
* When compared with ^{99}Tc^{m}-PYP $p < 0.025$.

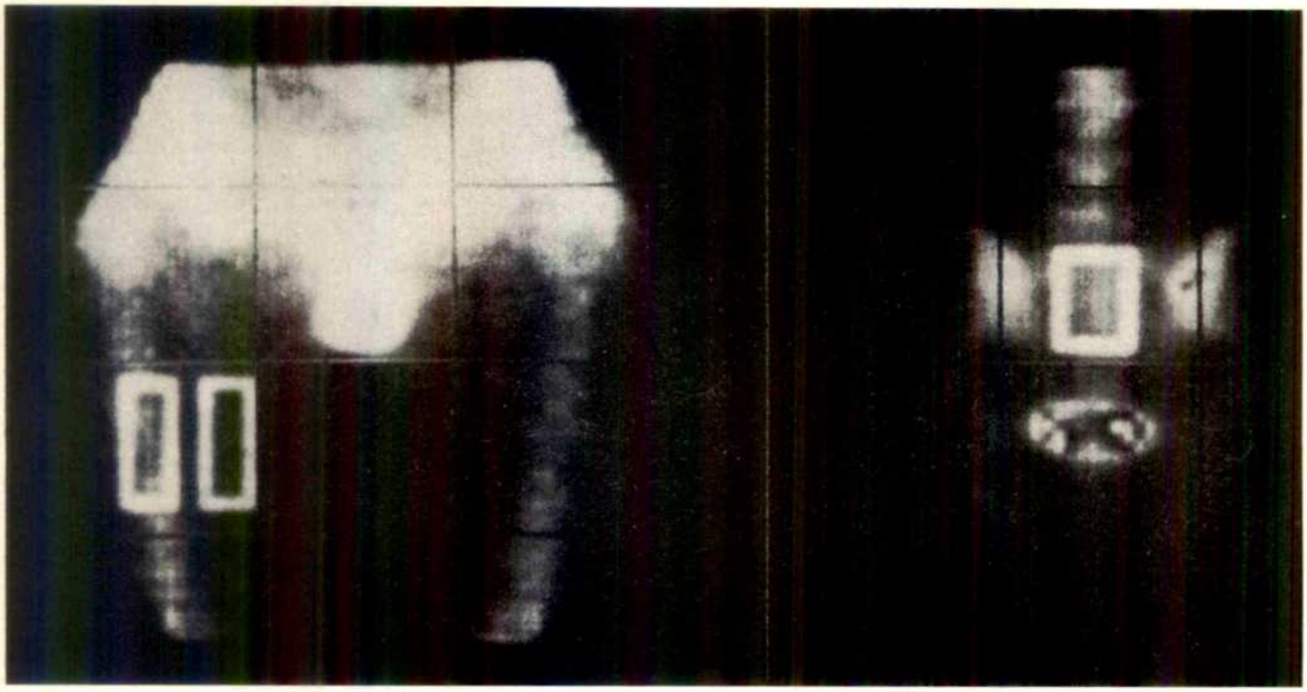

FIG. 1.

Areas used for setting regions-of-interest. Femur and soft tissue regions (anterior view; on the left) and os sacrum region (posterior view; on the right).

0.34 mg of stannous fluoride (the contents of one vial) (61 patients) or one third of these quantities (79 patients). ^{99}Tc^{m}-PYP was injected as an equal dose of ^{99}Tc^{m} pertechnetate, with 59.4 mg of pyrophosphate and 1.3 mg of stannous chloride (the contents of one commercial vial) (146 patients). Bone scintigraphy was started in one group of patients A ($n=137$) 1.5 h after injection and was finished not later than 2.5 h. In a second group of patients B ($n=149$) the examination was performed in the period from 2.5 h to 3.5 h after injection. These two groups were separated each into five subgroups according to the age of the patients: A, B (1) contains those between 20 and 39 years; (2) 40 to 49 years; (3) 50 to 59 years; (4) 60 to 69 years; (5) over 70 years. Taking into account the two different amounts of ^{99}Tc^{m}-MDP injected we obtained 20 subgroups of patients examined with ^{99}Tc^{m}-MDP (Table I) and ten subgroups of patients examined with ^{99}Tc^{m}-PYP (Table II). No patient from one subgroup was present in another subgroup. For each patient three different uptake ratios were computed (see Tables I, II and below).

Bone scintigraphy was performed with a wide field scintillation gamma camera* attached to a 48K computer system with a double disk store† enabling the ROI technique to be performed. Besides the routine scanning, two Polaroid photos were made, each exposed for three minutes and data was additionally stored on the disk in order to set ROI: (1) pelvis in posterior view and (2) lower pelvis together with both the thighs in anterior view (Fig. 1). The regions of interest were chosen to contain (a) the middle third of the right femur (compact bone), (b) soft tissues of the medial part of the thigh and (c) the mid part of the os sacrum (cancellous bone). The count rate

TABLE II

FEMUR-TO-SOFT TISSUE (F/ST), OS SACRUM-TO-FEMUR (S/F) AND OS SACRUM-TO-SOFT TISSUE (S/ST) RATIOS OBTAINED 1.5 H TO 2.5 H (A) or 2.5 H TO 3.5 H (B) AFTER INJECTION OF ^{99}Tc^{m} SN-PYROPHOSPHATE (PYP) IN 146 PATIENTS CLASSIFIED INTO DECADES OF AGE ((1) to (5)).

^{99}Tc^{m}-pyrophosphate (Mean ± S.D.)				
A	n	F/ST	S/F n=65	S/ST
(1)	12	1.46±0.18	3.00±0.71	4.38±1.10
(2)	10	1.48±0.21	2.93±0.58	4.34±0.80
(3)	21	1.47±0.21	2.47±0.47	3.83±0.73
(4)	11	1.46±0.19	2.61±0.51	3.81±0.56
(5)	11	1.34±0.16	2.49±0.41	3.34±0.58
B	n		n=81	
(1)	8	1.49±0.25	3.09±0.70	4.60±1.18
(2)	15	1.52±0.22	3.13±1.30	4.75±1.54
(3)	18	1.58±0.25	2.77±0.42	4.38±0.82
(4)	23	1.51±0.21	2.76±0.57	4.17±0.88
(5)	17	1.60±0.23	2.51±0.70	4.02±0.92

(1) 20–39 years of age
(2) 40–49
(3) 50–59
(4) 60–69
(5) >70
A 1.5 to 2.5 h after injection.
B 2.5 to 3.5 h after injection.

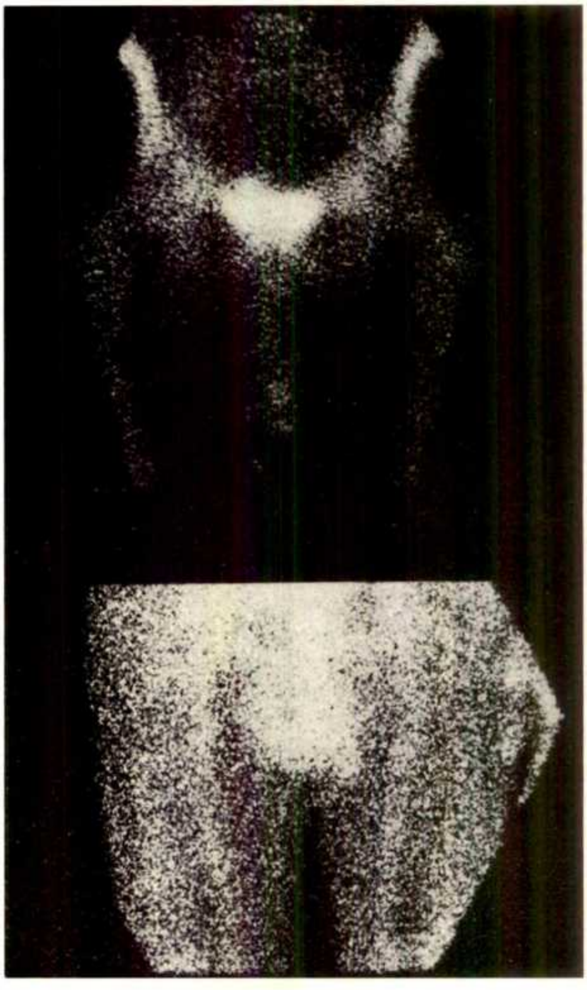

FIG. 2.

Pelvis and thighs imaged in anterior view in a 57-year-old male patient 2 h after injection of ^{99}Tc^{m}-MDP (1 vial). F/ST=1.80 proves small soft tissue accumulation (top). Same view in a 59-year-old male patient (bottom) 2 h after injection of ^{99}Tc^{m}-MDP (1 vial). Over-exposed image shows high soft tissue accumulation, especially in the interior areas of the thighs; F/ST=1.14.

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*Ohio-Nuclear, Series ON 110.

†Intertechnique, Cine 240.

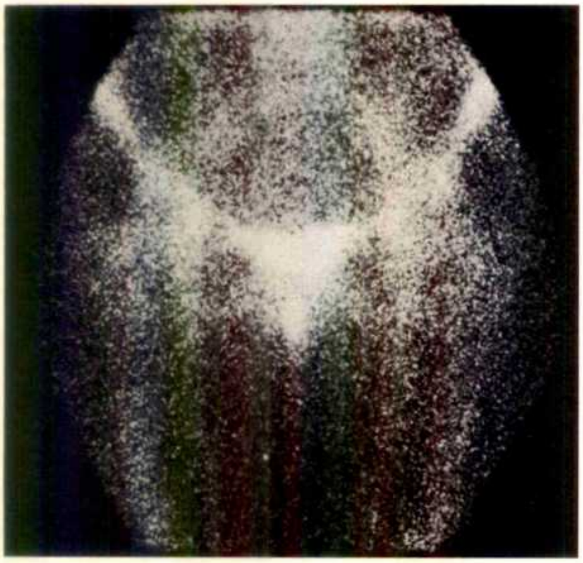


FIG. 3.

Pelvis and thighs imaged in anterior view in a 52-year-old female patient 2 h after injection of ^{99}Tc^{m}-PYP. F/ST = 1.54 indicates usual soft tissue accumulation in the interior part of the thighs.

density (total counts divided by the number of addresses enclosed by one region) derived from these three ROI were used to compute the values of three ratios: (1) a/b; (2) c/a; (3) c/b. Ratios for ^{99}Tc^{m}-MDP and for ^{99}Tc^{m}-PYP, obtained from similar regions, were compared using an unpaired "t" test. In addition, scintiphotos from the chest (anterior view) and the thighs were compared in order to detect accumulation of radioactivity in the myocardium, the bloodpool of the heart or in the liver as well as to determine the appearance of radioactivity in the medial part of the thigh (Figs. 2, 3).

RESULTS

^{99}Tc^{m}-MDP

Values of the ratios (1) to (3) are listed in Table I. There was no significant difference between patients injected with 5.0 mg MDP and the group which had received 1.7 mg. The ratios in group A (1.5 h to 2.5 h after injection) did not differ systematically from those in group B (2.5 h to 3.5 h after injection) although some of the individual ratios out of group B were somewhat higher than the corresponding values out of group A [see A (4, 5) versus B (4, 5)].

Mean values of ratio (1) (compact bone/soft tissue) from all subgroups of group A ($\bar{x}=1.64$) as well as from the subgroups of group B ($\bar{x}=1.73$) were smaller by factors of 3.45 (A) or 3.47 (B) than the mean values for ratios (3) (cancellous bone/soft tissue). A decrease in ratios with increasing age was found, especially in ratio (2) (cancellous bone/compact bone). Values of ratios (1) and (3) did not show this correlation to the same extent.

In no case could radioactivity be found in the heart or in the liver. A small region of accumulation of radioactivity in the area close to the great vessels of the thigh was imaged in 25 out of 91 patients (27.4%) examined 1.5 h to 2.5 h after injection and in 22 out of 85 patients (25.8%) examined 2.5 h to 3.5 h after injection (Fig. 2) (these patients were taken from both the "normal uptake group" and "pathologic skeletal uptake group").

^{99}Tc^{m}-pyrophosphate

Values of the ratios (1) to (3) are listed in Table II. All ratios in group A (1.5 h to 2.5 h after injection) were found to be smaller than the same ratios in group B (2.5 h to 3.5 h after injection). The relatively wide standard deviations of results in the subgroups did not allow this to be proved statistically for every single subgroup.

Mean values of ratio (1) from all subgroups of group A ($\bar{x}=1.44$) as well as from all subgroups of group B ($\bar{x}=1.55$) were found to be smaller by a factor of 2.74 (A) or 2.84 (B) than the mean values of all ratios (3). The decrease of ratios with increasing age was most obvious in ratio (3) of both groups A and B as well as in ratio (2) of group B.

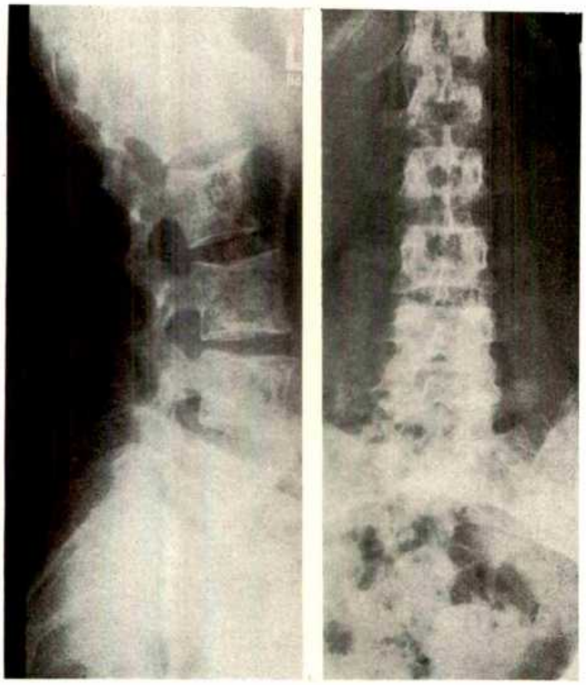
No radioactivity was ever found in the heart or in the liver. A small region of radioactivity in the area close to the great vessels of the thigh was imaged in 65 of 84 patients (77.3%) examined 1.5 h to 2.5 h after injection as well as in 66 of 90 patients (73.3%) examined 2.5 h to 3.5 h after injection (Fig. 3).

^{99}Tc^{m}-MDP versus ^{99}Tc^{m}-PYP

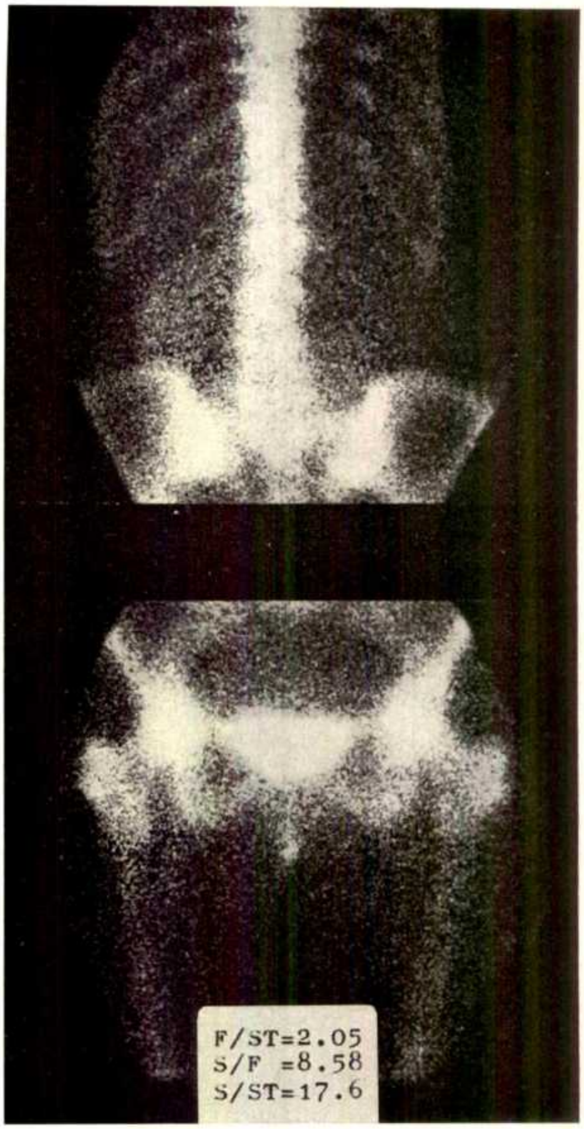
All corresponding ratios for ^{99}Tc^{m}-MDP turned out to be higher than for ^{99}Tc^{m}-PYP. Statistically significant differences ($p < 0.025$) were found for all ratios marked with an asterisk (*) in Table I. All ratios which were obtained with ^{99}Tc^{m}-MDP within 1.5 h to 2.5 h after injection were higher than the corresponding ratios obtained with ^{99}Tc^{m}-PYP 2.5 h to 3.5 h after injection. ^{99}Tc^{m}-MDP was taken up less in the non-target areas of the medial part of the thigh as is shown by the great difference of accumulated radioactivity imaged in this area. The amount of uptake in this region did not apparently decrease with increasing time after injection of either of the radiopharmaceuticals.

Ratios in patients with "pathologic pattern" of skeletal uptake

Of the 53 patients with proved osseous metastases or primary bone-tumours situated in the spine,



A



B

FIG. 4.

Breast cancer with diffuse bone-metastases in a 39-year-old female patient. X-ray examinations revealed multiple osteolytic defects in the lumbar spine (A). Bone scan (B) shows no distinct area of increased or decreased accumulation of ^{99}Tc^{m}-MDP (2 h after injection; ⅓ vial). Highly increased ratio values (bottom; for normal values see Table I) of S/F and S/ST indicate augmented uptake in the os sacrum (and in the other parts of the spine imaged) confirming the radiologic diagnosis.

pelvis or femur, only seven patients (13.2%) had uptake ratios greater than 2 S.D. above the mean values listed in both Tables I and II without an associated "pathologic" focal pattern of uptake inside the ROI areas (Fig. 4A, b). In patients receiving long-term haemodialysis ($n=6$) all ratios were also above these upper limits (Fig. 5). This could be explained by the well known bone disease that occurs with this treatment (Simpson *et al.*, 1976).

DISCUSSION

Comparative data on ^{99}Tc^{m}-Sn-pyrophosphate, ^{99}Tc^{m}-Sn-ethylenehydroxy-diphosphonate and ^{99}Tc^{m}-Sn-methylene-diphosphonate in respect of their bone seeking properties in animals have been published by Subramanian *et al.* (1975). It was found that ^{99}Tc^{m}-MDP has the most rapid clearance from the blood and soft tissues as well as the highest urinary excretion within the first few hours after injection. Uptake into the femur and the pelvis was noticeably higher with ^{99}Tc^{m}-MDP than with the ^{99}Tc^{m}-PYP. Our own data obtained from a series of experiments with rabbits (Büll *et al.*, 1974) where the concentration of ^{99}Tc^{m}-PYP in bone, muscle and blood was measured, showed higher target non-target ratios than in the study cited above. This could depend on the different composition of the kits because the CIS-kit used was definitely superior to the Mallinckrodt-kit used by Subramanian *et al.* (1975), (Büll *et al.*, 1975). On the other hand it is well known that with ^{99}Tc^{m}-PYP bone/soft tissue ratios are greater when more pyrophosphate is injected (Schümichen *et al.*, 1974) up to a limit (Eckelman *et al.*, 1974). Having this in mind, we used a high dose of pyrophosphate, *i.e.* the complete contents of one commercial vial (59.4 mg) per patient.

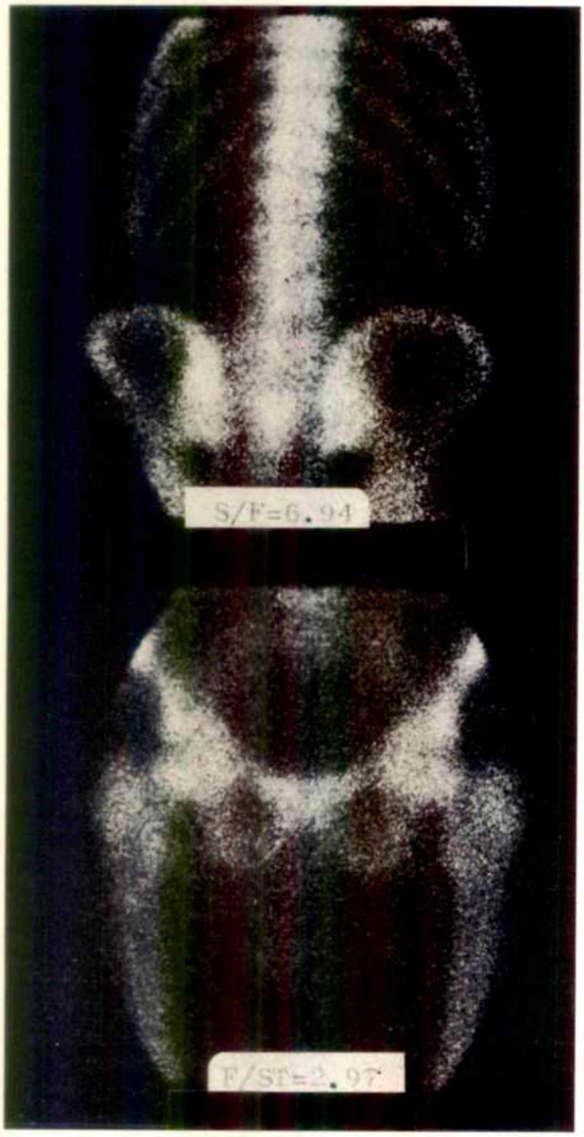


FIG. 5.

39-year-old male patient receiving long-term haemodialysis. Highly increased ratio values (S/F and F/ST; for normal values see Table I) computed 2 h after injection of ^{99}Tc^{m}-MDP (⅓ vial) indicate augmented skeletal uptake in both os sacrum and femur. No correlate was found in the X-ray examination.

Comparison of bone scans on Polaroid or X-ray film can only be done subjectively in different patients and with various radiopharmaceuticals. More objective information can be gained if the region-of-interest technique is used, where values of uptake ratios in different tissues can be applied to express the contrasts appearing in a bone scan.

The ROI, framing the femoral diaphysis encloses both bone and soft tissue, the latter situated in front of and behind the femur. The soft tissue radioactivity could not be subtracted but we think that it does not really interfere with the count rate derived from the bone because of the low radiation energy of ^{99}Tc^{m}. This prevents the detection of radiation from behind the femur. The reference area of the os sacrum used, *i.e.* that part which is situated between the iliosacral joints (excluding the joints *per se*) (Fig. 1), is representative of cancellous bone without too much soft tissue interference.

Results obtained from the present study confirm higher uptake of ^{99}Tc^{m}-labelled phosphate complexes in cancellous bone than in compact bone. Considering the factors which influence the skeletal uptake of these compounds (capillary permeability, local bone blood flow, the presence of immature collagen, size of osseous surface; Büll *et al.*, 1975; Garnett *et al.*, 1975; Genant *et al.*, 1974; Kaye *et al.*, 1975; Siegel *et al.*, 1976; Wiegmann *et al.*, 1976) this preference for cancellous bone is well understood. ^{99}Tc^{m}-MDP in the cancellous bone was incorporated 3.45 fold (1.5–2.5 h after injection) and 3.47 fold (2.5–3.5 h after injection) better than in compact bone, if the mean values of all groups A (1) to (5) or B (1) to (5) were compared. With ^{99}Tc^{m}-PYP, the corresponding factors of 2.74 and 2.84 were computed. These results indicate (a) that there is no dependence of the cancellous/compact bone ratio on increasing time after injection and (b) that these ratios are significantly higher with ^{99}Tc^{m}-MDP. If the bone/soft tissue ratios are considered it is apparent that they are higher for ^{99}Tc^{m}-MDP than for ^{99}Tc^{m}-PYP. More statistically significant differences were found on comparing cancellous bone/soft tissue ratios than with compact bone/soft tissue ratios (see asterisks in Table I). It is more likely that the higher cancellous bone/compact bone ratios with ^{99}Tc^{m}-MDP are caused by an augmented uptake of this radiopharmaceutical in the cancellous bone.

Moreover, it is obvious that soft tissue accumulation with ^{99}Tc^{m}-PYP is higher than with ^{99}Tc^{m}-MDP. This is supported by the fact that the imaging of soft tissue uptake in the area of the medial part of the thigh with ^{99}Tc^{m}-PYP was three times as frequent as with ^{99}Tc^{m}-MDP. This accumulation was mostly correlated with the imaging of an area which is close to the great vessels of the thigh (Figs. 2, 3). In contrast, no radioactivity was visible in the heart or in the liver despite the fact that the bloodpool-volumes of these organs are much larger. Therefore it is of interest as to whether this accumulation in the thigh is due to radioactivity in the bloodstream. There was no decrease of the percentage of imaged activity in this area of accumulation with increasing time after injection. From Subramanian's study (Subramanian *et al.*, 1975) we know that in man (a) a decrease of blood radioactivity occurs with both of the radiopharmaceuticals with increasing time after injection and (b) that only some 8% of administered radioactivity is left using ^{99}Tc^{m}-PYP or 3% using ^{99}Tc^{m}-MDP in the total circulating blood, three hours after injection. Hence it is more likely that this accumulation is part of an uptake in tendons, in other collagen-containing tissues of the thigh and/or in the sheath and wall of the vessels than in the circulating blood. With ^{99}Tc^{m}-PYP a relatively high uptake in tendons and fasciae has been demonstrated in rabbits (Büll *et al.*, 1974) as well as with ^{99}Tc^{m}-EHDP in rats (Silberstein *et al.*, 1975). In man, soft tissue accumulation was observed in a variety of benign diseases (Büll *et al.*, 1975), for example in calcification of soft tissues, as well as in some malignant tumours (Poulose *et al.*, 1975).

Poulose *et al.* (1975) found increased concentrations of ^{99}Tc^{m}-PYP in the knee joints of patients above 70 years of age and stated "that this property is related to age and therefore, inversely related to bone density". An interesting finding in the present study is the decrease of cancellous bone/compact bone ratios with increasing age. This was routinely found with both of the radiopharmaceuticals examined (Table I, II; S/ST). Compact bone/soft tissue uptake ratios remained nearly constant, whereas cancellous bone/soft tissue ratios tended to decrease. These findings were much more evident in female patients than in male patients. Taking into account that no absolute concentrations were determined by these three ratios the most likely explanation to account for such changes is a decrease of uptake in the cancellous bone with increasing age. This correlates directly with the rarefaction of cancellous bone structure, *i.e.* loss of bone-surface, as is well known by radiologists in elderly patients.

The results of this study indicate that all uptake ratios calculated with ^{99}Tc^{m}-MDP are higher than with ^{99}Tc^{m}-PYP. The superiority of the Technetium MDP bone agent is shown additionally by the fact that higher uptake ratios with ^{99}Tc^{m}-MDP are observed 1.5 to 2.5 h after injection than with ^{99}Tc^{m}-PYP, 2.5 h to 3.5 h after injection. The need to wait at least three hours to obtain good quality images when using ^{99}Tc^{m}-PYP (Snow and Weber, 1975) is not necessary when using ^{99}Tc^{m}-MDP. Moreover, when using ^{99}Tc^{m}-MDP, the ratio values and therefore the image quality does not depend on the amounts of MDP injected (Table I).

The ROI technique is designed to reveal diagnostic relevance in those cases where all parts of the imaged skeleton accumulate higher than normal amounts of bone seeking agents (Fig. 4, 5). The absence of an optical reference of normal skeletal uptake in a scintiphoto is replaced by ratio values derived from various regions of interest. Soft tissue accumulation in ^{99}Tc^{m}-MDP is smaller and more constant than in ^{99}Tc^{m}-PYP which enables the more reliable use of this parameter for a reference value.

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Book review

Practical Radioimmunoassay. By A. J. Moss, Jr., Glenn V. Dalrymple, and Charles M. Boyd, pp. ix+158, 1976 (The C. V. Mosby Company, Saint Louis; London, Henry Kimpton), £9·70.

In most countries there is still no control of the quality of commercial diagnostic kits and the would-be user must select between a number of kits which will not necessarily all be of a satisfactory quality. *Practical Radioimmunoassay* is written for the intending purchaser or user of such kits. The technique of radioimmunoassay permits estimation of a selected substance, present in minute amounts only, in a mixture of closely related substances. The purchaser of a kit needs sufficient information to evaluate the suitability of what is being supplied. Estimates are unlikely to be valid unless made with reagents of suitable quality and stability, selectively matched to give an assay system which estimates only the substance intended without interference from other substances which may be present in test samples in variable amounts. The kit user also needs assurance that there will be continuity of estimates with successive batches of reagents. A satisfactorily robust system will give essentially similar estimates of potency when the same samples are tested in different laboratories or by different operators. Excellence of laboratory technique cannot compensate for inappropriate materials; an appreciation of likely pitfalls and problems is essential both for generation of valid estimates and for comment on their interpretation.

The book *Practical Radioimmunoasaay* belies its title. It is not so much a practical manual as a compendium of information related to performance of radioimmunoassays. Topics covered include the structure of the atom and modes of radioactive decay, detection of radiation and details of operation of a typical counter. Elementary statistical methods and the consideration of how long to count occupy 21 out of the 140 pages of text. Although it is acknowledged that radioiodinated peptide tracers are unlikely to be prepared in a laboratory dependent upon assay kits, this section illustrates the patchy nature of the text. A procedure for radioiodination is described in detail but the section on purification of tracer antigens is written in more general terms and no mention is made of the essential need for carrier protein to prevent unwanted surface adsorption of trace amounts of peptides. Criteria for assessment of labelled antigens are located unexpectedly in a chapter on "Quality control and normal ranges". In discussion of separation systems, the reader is properly advised to "verify the performance of each particular separation for any given assay" but receives no guidance on how this might be done.

The essentials of radioimmunoassay are dealt with so cursorily that *Practical Radioimmunoassay* will not help the assayist to recognize when or why an assay system does not function properly and it will be of little use to the many clinicians and laboratory workers who seek succinct instruction in this versatile technique.

P. Mary Cotes

1977, *British Journal of Radiology*, *50*, 637–644 SEPTEMBER 1977

Verification and recording of radiotherapy treatments using a small computer

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ABSTRACT

A small computer has been interfaced to a linear accelerator used for routine radiotherapy. The objectives are to assess the rate and magnitude of some of the mistakes which may occur, to prevent these where possible and to assist radiographers with record keeping. In this paper we describe our approach to the problem, the apparatus used, the computer program, and the results of several years of operating experience while the system was continually being developed. On one linear accelerator, we estimate that an error has been prevented roughly once in every 500 field parameters set. The most common error is in setting the diaphragms and a detailed analysis is given of possible reasons. Doses in monitor units are recorded automatically and a running total of cumulative dose is maintained; plans for the printing of the dose in rads at selected points are discussed.

Digital computers are now widely used for a number of tasks in radiotherapy and proposals for their use in the monitoring and automation of therapy machines were discussed several years ago (Glicksman and Nickson, 1971; Herring *et al.*, 1972; McKinley, 1971; Rosenow and Seidl, 1971; Umegaki, 1971). A number of commercial companies have produced systems which have been tried out in a few radiotherapy centres although some of these systems use "hard-wired" logic rather than a general purpose programmable computer. There are two main alternative approaches: one is essentially a checking system sometimes called "select and confirm" which allows verification and recording of each treatment, the other includes the total automatic control of movements and set-up. At the Royal Marsden Hospital, we have designed and introduced an experimental system of the first kind using a small digital computer linked to a linear accelerator. The basic philosophy has been to modify the normal routine of radiographers as little as possible and therefore the new system has been used only for checking, verification and recording, and no attempt has been made to control the movements automatically.

EQUIPMENT AND PROGRAM

The therapy machine is an SL75–10 (Philips) linear accelerator. Machines of this type are now fitted with data read out as a standard facility. This produces voltages which are directly proportional to continuously variable parameters such as the diaphragm openings and angles together with digital outputs for the discrete quantities such as dose, time, wedge filter and modality. An interface which includes a ten bit analog to digital converter and eight way multiplexer has been constructed to connect these signals to the computer. Figure 1 shows a block diagram of the system. The computer is a PDP8E (Digital Equipment Company) chosen for low cost, comparatively simple interfacing and compatibility with other computers in the hospital which are used for radiotherapy dose calculations (prototype RAD–8) (Bentley and Milan, 1971) and for nuclear medicine. The machine has 8192 words of core store (12 bits per word) and two miniature magnetic tape units (DECtape type TU56, Digital Equipment Company) each with a capacity of 188000 words. One tape is used to record patient data and the other provides an effective extension of core capacity by using program overlays. This form of backing store (DECtape) was chosen in preference to floppy discs or convential discs in the belief that it offered the highest reliability at a reasonable cost. Subsequent experience with this and our other computer systems which do use discs has shown that the DECtape does in fact have a lower failure rate. The disadvantage of DECtape is the longer access time but this is overcome by programming techniques which make program overlay virtually instantaneous and reduce the data access time to less than five seconds in most circumstances.

There are two terminals for communication with the computer. The first of these is a conventional Teletype (Data Dynamics Model 390) and this was all that was available in the first operating version of the system. It was found to be too slow and too noisy and a Visual Display Unit (Beehive Model II) together with a fast and silent paper tape reader (Data Forster Model 1303), were subsequently added. Figure 2 shows the position of the visual display monitor keyboard and tape reader. The Teletype has been retained to produce permanent records but removed to a point about ten metres away from the control desk, still accessible to radiographers but normally out of earshot.

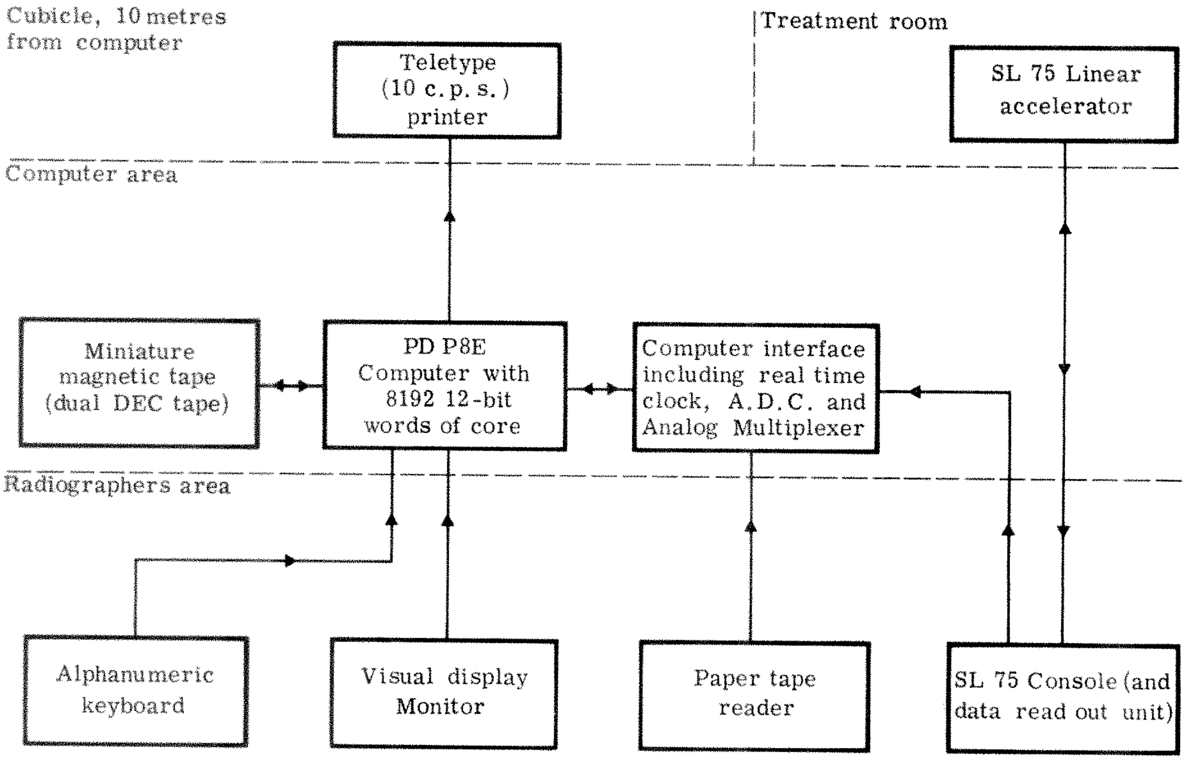

Cubicle, 10 metres from computer
Treatment room
Teletype (10 c.p.s.) printer
SL 75 Linear accelerator
Computer area
Miniature magnetic tape (dual DEC tape)
PD P8E Computer with 8192 12-bit words of core
Computer interface including real time clock, A.D.C. and Analog Multiplexer
Radiographers area
Alphanumeric keyboard
Visual display Monitor
Paper tape reader
SL 75 Console (and data read out unit)

Fig. 1.
Block diagram of the system.

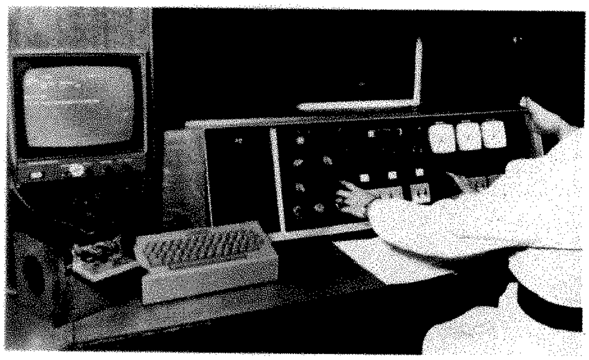


Fig. 2.
Therapy control desk with visual display monitor, keyboard and tape reader.

All programming is in Assembly Code (PAL–8). This results in economies of core and allows the development of efficient overlay techniques which would not be possible with a high level language such as Fortran. It also facilitates use of the interrupt feature of the PDP8 for a real time clock and allows characters printed by the Teletype to be buffered, thereby preventing the main program from being slowed down.

Treatment verification program

The flow diagram, Fig. 3, shows the essential features of the main program. Patients are identified to the computer by typing in the six digit hospital number. This is used by the computer to retrieve information about the patient's treatment. If no information has been previously entered the computer requests the entry of a paper tape. The data on this tape are then transferred to magnetic tape, avoiding the need for subsequent re-entry.

After the patient has been identified and, where necessary, a paper tape entered, the computer requests the identity of the field to be treated. This is given by typing a short mnemonic based on codes already used by the radiographers *e.g.* LLAT for left lateral or RAO for right anterior oblique.

The computer is now able to begin a continuous comparison of the set up and the parameters required for the selected field. It produces no indication of the result of this comparison until an attempt is made to start the treatment. If there is no discrepancy the display on the screen does not change until treatment is terminated. At the end of each treatment a single letter command is needed to allow selection of the next field for the same patient or

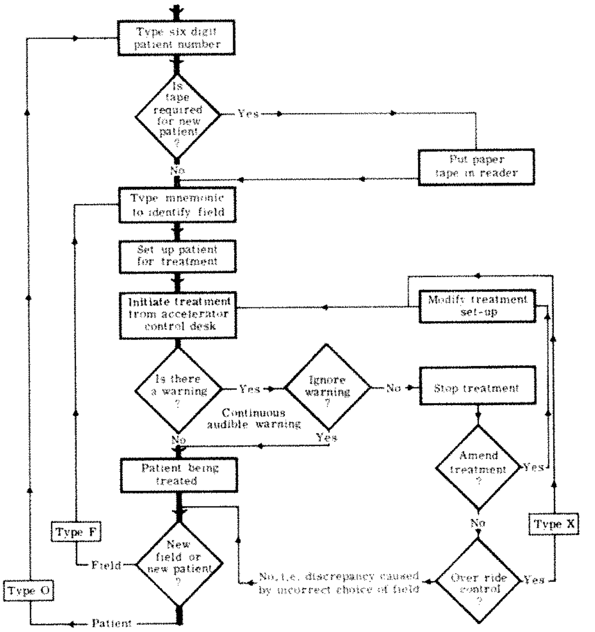

Type six digit patient number
Is tape required for new patient ?
Yes
No
Put paper tape in reader
Type mnemonic to identify field
Set up patient for treatment
Initiate treatment from accelerator control desk
Modify treatment set-up
Is there a warning ?
Yes
Ignore warning ?
No
Stop treatment
Continuous audible warning
No
Yes
Patient being treated
Amend treatment ?
Yes
No
Type F
Type X
Type O
Field
New field or new patient ?
No, i.e. discrepancy caused by incorrect choice of field
Over ride control ?
Yes
Patient

FIG. 3.

Simplified flow chart of the system as it appears to the radiographer.

selection of the next patient. There is no constraint on the order of treatment of fields or of patients.

The thick line on Fig. 3 shows the normal flow in the absence of a discrepancy. In the event of a discrepancy between the data on the tape and the set-up, an audible warning is given in the form of an intermittent tone. This occurs immediately the start treatment button is pressed at the accelerator console and persists until the button is released. There is no automatic inhibition of treatment. As there is a delay of a few seconds between pressing the button and the beam coming on, there is ample time to prevent treatment. The treatment could, in fact, be continued, ignoring the warning, but if it were, the very obvious audible signal would persist throughout the treatment. This course of action has never been taken.

When there is a discrepancy, information is given on the screen in the form of one of the messages in Table I, but quantitative details are only given on the print out. The radiographer should now recheck the set-up against the treatment plan. If the set-up is found to be incorrect, it is changed and a new attempt to start treatment is made. If, on examination, the set-up is found to be correct, the radiographer may override the control by a single command from the keyboard. Every use of the override is logged and there is no restriction on its use except that it cannot be used *before* the occurrence of an error message. If the discrepancy is due to incorrect identification of the field, it may be re-selected after typing the end of treatment command.

TABLE I

ERROR MESSAGES

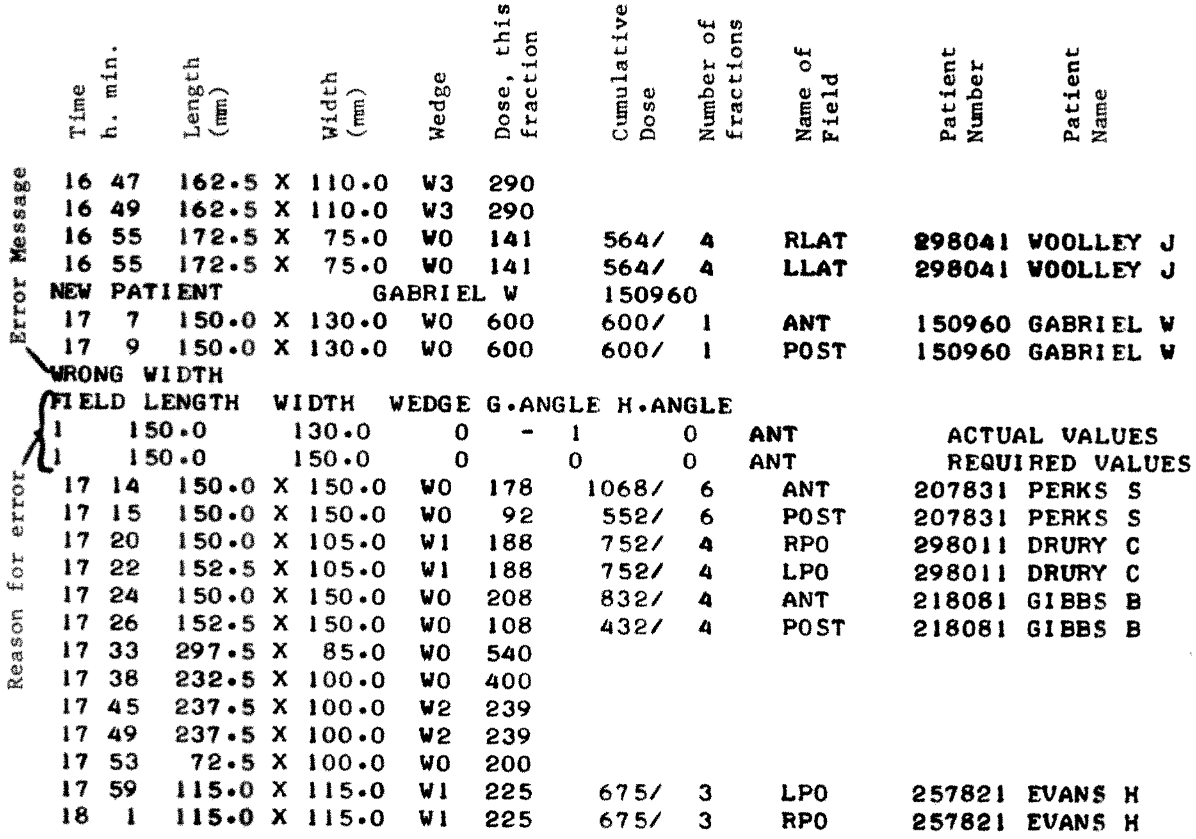
Wrong length
Wrong width
Wrong wedge
Wrong wedge direction
Wrong gantry angle
Wrong head angle
Multiple errors are grouped in a single line message, *e.g.* Wrong length, width, gantry angle.

The checking sub-routine takes account of both collimator and gantry orientations in assigning the measured openings of the collimator jaws to the parameters length and width so that they can be defined with respect to the patient. This will prevent the turning of the collimator for square fields by 90 deg. and for rectangular fields by 180 deg. from being signalled as errors, provided of course there is no wedge filter. In a similar way, when a wedge is present an error of 180° in the orientation of the collimator will be signalled as a wedge direction fault.

The paper tape is produced by an additional program on the treatment planning computer and it has been coded in such a way that all the data for up to six fields can be packed into a paper tape whose total length does not exceed 30 cm. This duplicates the normal channel of communication from planning to therapy. If any parameters are changed during a course of treatment, a new tape is produced which can be entered by one of the sub-programs discussed later.

Dose recording

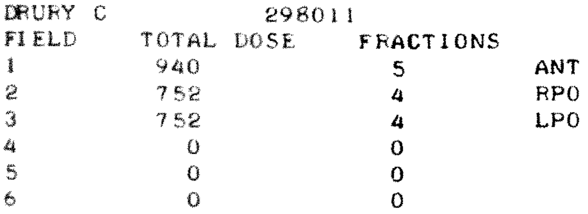
The computer updates a permanent treatment record file on magnetic tape at the end of each treatment and also prints a single line record of the field just treated. The printed record includes the time of treatment, patient and field identity, field size, wedge filter and dose just given, as well as the cumulative dose and the number of treatments so far for that field (Fig. 4). This record forms a daily log for the accelerator, and more than satisfies the Code of Practice (H.M.S.O. 1972) requiring all treatment machines to have an automatic record of dose and wedge filter for each treatment. A similar log is maintained as a matter of course by the radiographers in addition to the patient's treatment record.



```
Time    Length      Width   Wedge Dose,    Cumulative Number of Name of   Patient  Patient
h. min. (mm)        (mm)          this     Dose       fractions Field     Number   Name
                                  fraction
16 47   162.5 X 110.0   W3    290
16 49   162.5 X 110.0   W3    290
16 55   172.5 X  75.0   W0    141       564/   4      RLAT       298041 WOOLLEY J
16 55   172.5 X  75.0   W0    141       564/   4      LLAT       298041 WOOLLEY J
NEW PATIENT          GABRIEL W         150960
17  7   150.0 X 130.0   W0    600       600/   1      ANT        150960 GABRIEL W
17  9   150.0 X 130.0   W0    600       600/   1      POST       150960 GABRIEL W
WRONG WIDTH
FIELD LENGTH     WIDTH    WEDGE G.ANGLE H.ANGLE
1       150.0     130.0      0    -   1       0    ANT       ACTUAL VALUES
1       150.0     150.0      0        0       0    ANT       REQUIRED VALUES
17 14   150.0 X 150.0   W0    178      1068/   6      ANT        207831 PERKS S
17 15   150.0 X 150.0   W0     92       552/   6      POST       207831 PERKS S
17 20   150.0 X 105.0   W1    188       752/   4      RPO        298011 DRURY C
17 22   152.5 X 105.0   W1    188       752/   4      LPO        298011 DRURY C
17 24   150.0 X 150.0   W0    208       832/   4      ANT        218081 GIBBS B
17 26   152.5 X 150.0   W0    108       432/   4      POST       218081 GIBBS B
17 33   297.5 X  85.0   W0    540
17 38   232.5 X 100.0   W0    400
17 45   237.5 X 100.0   W2    239
17 49   237.5 X 100.0   W2    239
17 53    72.5 X 100.0   W0    200
17 59   115.0 X 115.0   W1    225       675/   3      LPO        257821 EVANS H
18  1   115.0 X 115.0   W1    225       675/   3      RPO        257821 EVANS H
```

FIG. 4.

Sample of daily log, patient name and number omitted in case of unmonitored treatments.



```
DRURY C             298011
FIELD      TOTAL DOSE      FRACTIONS
1             940              5          ANT
2             752              4          RPO
3             752              4          LPO
4               0              0
5               0              0
6               0              0
```

FIG. 5.

Patient treatment summary.

At present the treatment summaries which can be obtained for each patient on the screen and the printer are limited to the cumulative dose for each field and the number of daily sessions in which the dose was given; it is given only in monitor units. Figure 5 shows an example. Clearly this is inadequate and we are currently expanding it to a complete record, giving the date and the daily dose in rad at selected points, thereby duplicating the normal hand-written record. Until the dose recording part of the program is completed, the system is used only for patients who have multi-beam treatments planned on the treatment planning computer. For the rest, a printed summary is still produced but without patient identity and cumulative dose. Some of the cases in Fig. 4 are of this kind.

Other programs

As well as the treatment program which is initiated by identifying the next patient, there are a number of "sub-programs" which are called by typing a single letter. Most of these programs are concerned with the re-call of data, such as details of a patient's treatment plan, his treatment so far, or lists of the patients on treatment. New paper tapes for modified treatment plans are also entered using a sub-program.

Ease of use

Throughout the development of the system it was clear that it was essential to minimize the effort of operation if it was to be used on a routine basis on an accelerator treating daily on average 50 patients involving about 80 separate fields. Typing has been kept to the minimum of the six digit hospital number to identify the patient, the short mnemonic to identify each field and a single letter command after each field is treated.

Extra commands or responses will be needed in the event of any departure from the correct operating sequence of patient and field identification, successful verification and treatment, and signalling the end of treatment. These may be single letters or the answer "Yes or "No". The text on the screen is designed to guide the user as much as possible. The use of the six digit hospital numbers which appear prominently on the treatment sheets has proved entirely acceptable. This has avoided typing the long strings of letters which occur in names.

The use of mnemonics to identify fields has been found preferable to the use of field numbers. Numbers were used in earlier versions of the program but were found to cause confusion over field identification and led to frequent spurious signalling of discrepancies. Little difficulty has been experienced in the use of letters provided they are used singly or in very short strings.

Early versions of the program required entry of paper tape for each patient attendance. The frequent repetition of this operation and the need to store the tapes between treatments were not entirely acceptable. The use of the paper tape only on occasions when new data are required reduces the total number of tape entries approximately tenfold and avoids the need for its subsequent storage. There appears to be little need for the paper tape as an aid to identification of the patient; the use of the hospital number with automatic re-call and display of the patient's name has so far proved adequate.

CLINICAL EXPERIENCE

The accelerator on which the system is being developed has had a substantial routine commitment since before the inception of the project. The introduction of the computer has been very gradual and a careful balance has always been struck between the ease of use of the system in any current phase of development and the number of patients monitored. Throughout its introduction it was emphasized that the project was experimental, that the co-operation and tolerance of the radiographers would be sought and that serious attention would be given to their comments and suggestions.

Early clinical experience

The first tentative steps were taken in 1973 in arranging a very short trial of six weeks in which only seven patients were monitored. At that time the hardware was limited to the computer with only 4096 words of core, a Teletype (including a slow paper tape reader) and a light panel which displayed appropriate instructions under computer control.

After the first trial the system was withdrawn and substantially modified by the addition of the Visual Display Unit and the fast paper tape reader, and by increasing the core capacity to 8192 words. The Teletype could then be moved to a more distant site where it would cause less disturbance.

The system was reintroduced in 1974 for an indefinite period, but on the understanding that the number of patients monitored would be restricted until the system was completely acceptable. Substantial improvements were made to the program whilst it was in use but it became clear that some form of mass storage was needed to eliminate the repeated entry of paper tape for each patient attendance and the dual drive DECtape was added.

RESULT

In September 1975, when the system had evolved to the stage described, the regular analysis of errors was started. Tolerances are allowed in the checking program; these have been set to ±6° for angle and ±1 cm for field size. This avoids the unnecessary signalling as errors of small and unimportant differences.

Errors prevented

Table II classifies the discrepancies detected in 5533 fields in a 16-month period. It will be seen that there are relatively few errors in each class. The 19 cases where the field size was wrong are summarized and classified into five groups in Table III. In group 1 (seven cases) it was clear that the diaphragm settings had remained unchanged from the last treatment. In group 2 (two cases) the field dimensions set were those of another field for the same patient. The one case in group 3 was attributable to an inversion of length and width, and the one in group 4 occurred when one patient with a common

TABLE II

POTENTIAL ERRORS DETECTED AND PREVENTED

Incorrect field size	19
Incorrect gantry angle	5
Incorrect wedge	1
Incorrect wedge direction	8
	33

5533 fields monitored (25.9.75 – 8.2.77)

TABLE III

INCORRECT FIELD SETTINGS

Group	*Date*	*Set (cm)*	*Required (cm)*
		1 × b	1 × b
1. Field size as previous treatment	7.10.75	16.0 × 12.75	16.0 × 11.0
	11.2.76	15.25 × 9.0	9.0 × 8.0
	14.5.76	15.25 × 10.5	15.0 × 8.0
	8.6.76	15.0 × 15.0	18.0 × 10.5
	18.11.76	15.0 × 11.0	17.5 × 15.0
	8.12.76	14.25 × 14.0	16.0 × 10.5
	20.1.77	20.5 × 16.0	20.0 × 13.0
2. Field size as other field on same patient	1.4.76	14.25 × 13.0	13.0 × 13.0
	23.4.76	10.5 × 7.0	10.5 × 10.0
3. Length/breadth reversed	18.6.76	9.25 × 14.0	14.0 × 9.0
4. Two patients same surname	17.1.77	15.25 × 13.0	16.0 × 16.0
5. Other causes			
(a) Length only wrong	21.5.76	16.0 × 10.5	18.0 × 10.5
	12.11.76	15.0 × 6.0	12.0 × 6.0
	24.11.76	13.0 × 10.0	12.0 × 10.0
(b) Breadth only wrong	11.3.76	9.25 × 11.0	9.0 × 8.5
	7. 10.76	16.25 × 16.0	16.0 × 14.0
	7.12.76	15.0 × 13.0	15.0 × 15.0
	22.12.76	13.0 × 8.5	13.0 × 11.5
(c) Both wrong	24.5.76	11.5 × 8.0	9.5 × 6.5

TABLE IV

FALSE ERROR SIGNALS

A. Non-Intrinsic *i.e.* resulting from miscalibration of data readout or temporary software fault following program revisions.	40
B. Intrinsic *i.e.* resulting from misuse of system.	
(1) Field incorrectly identified	31
(2) Plan altered after tape made	5
(3) Tape out of date	20
(4) New tape used too soon	1
(5) Error in tape production	31
	88
Total false errors	128

5533 fields monitored (25.9.75 – 8.2.77)

surname was set up with the field sizes of another of the same surname.

The last group, 5, shows that there are cases for which an alternative explanation is needed. Field sizes are normally specified in steps of 5 mm whilst the computer print out gives the field setting to a precision of 2.5 mm. In many of the discrepancies where the required field size in centimetres was an integer the size actually set was also an integer. This suggests that incorrect settings may result either from misreading the dials or an aberration in transferring data from the treatment sheet.

The number of gantry angle errors was too few to draw any firm conclusions. Most were missettings of ten degrees. The wrong wedge was selected on only one occasion. This resulted from a transcription error in copying from the treatment plan to a secondary list used for setting up; in this case the error would probably have persisted but for the computer, for as long as the plan was used. On eight occasions the wedge sense was reversed.

False error signals

Table IV lists a total of 128 false error signals, cases where the system signalled an error but there was subsequently found to be none. Some cases of this kind are inevitable in a new and evolving system but this figure would be too high for a fully developed system when seen in relation to the figure of 33 true errors. The false errors are divided into two groups. The first group of 40 cases is attributable to hardware and software problems which have now been rectified although cases due to software errors occasionally arise when revised versions of the program are first run. In practice these troubles are usually detected and corrected within a few hours; they are included in our figures for completeness.

The other false errors are likely to recur because they are the result of incorrect use of the system, either in preparing and entering field data, or in communicating with the system at the time of treatment.

Calling the wrong field is the most frequent trouble at treatment time. Most often this occurs when a pair of symmetrical lateral or oblique fields are to be treated on the same day. The radiographer selects one of these fields before entering the treatment room to set up the patient, and as a result of the initial position of the accelerator chooses to treat the other field first without re-identifying it.

Incorrect data on tape is also a cause of false error signals. Data may be incorrect at the time of treatment for the following reasons:

1. A small change may be made in the length of the target volume after the plan is made. In such cases it is common practice to recalculate the dose at points without requesting a complete new

distribution. This may lead to a delay in producing a new paper tape until after the signalling of a false error.

2. The overall treatment strategy often consists of a number of phased plans. The production and entry of tapes for these various plans can get out of step with the treatment. Sometimes the tape lags behind treatment, although in one case the new tape was entered prematurely.
3. The tapes are produced at the planning computer, but the program which does so was not directly linked to the treatment planning program during the period of these results and data had to be entered manually. The person producing the tapes can make a mistake and in view of this the two programs are now linked thereby reducing the amount of data to be entered by hand.

Most of the false errors resulting from incorrect data follow from our emphasis that the data tape is produced on the planning computer. It would have been very much simpler to have used the first treatment as the source of input data but this approach has been rejected as it does not duplicate the communications chain from planning to treatment. An option to produce tapes does exist on the checking computer and can be used if no treatment planning computer is available.

DISCUSSION

There have been many proposals for automatic radiotherapy systems, most of which obtain their initial input data from either a simulator or the first treatment on the therapy machine. Our system may be unique in obtaining the data from a treatment planning computer and in so doing provides a complete duplicate pathway for information flow from planning to treatment.

The system described in this paper is a combination of prospective and retrospective checking. The set-up parameters are checked prospectively in time to make adjustments if the check reveals an error but the dose set is not included. A function of the computer is however to maintain a record of the dose actually given for retrospective comparison with the manual record. It would be feasible to check the dose prospectively by including dose data on the paper tape and very little modification of the program would be necessary to enable this to be done. This is not however practicable because the dose is not known by the technician or radiographer who prepares the treatment plan and the paper tape. In addition, the dose is subject to fairly frequent review during treatment. Furthermore, it is generally easier to correct in a later fraction for errors in dose than for errors in set-up parameters.

It is necessary to consider whether the checking system itself influences the possibility of errors. If the existence of the system leads to greater vigilance, we will underestimate the potential error rate. Also, the computer may lead to a subconscious but systematic change in working methods if it reveals to the radiographer particular areas in which mistakes are made: for example, greater care may be taken in setting field sizes. On the other hand, knowledge that a system to detect errors exists could result in a relaxation of effort and cause us to overestimate the potential error rate. It is difficult to determine which of these effects will predominate, but assuming they are small effects our results probably provide a useful guide to typical error rates with unmonitored treatments.

Our relatively small sample has shown that one mistake is prevented in about 170 set-ups. There are five monitored parameters per set-up but the detected error rate is one in every 710 parameter settings after allowing for the fact that multiple errors may sometimes occur (Table III). Even this is an underestimate because, in many treatments, pairs of fields with the same diaphragm settings are given in the same session and an error found for the first field would probably have been repeated in the second. After allowing for this, the estimated potential error rate is 1 in 515 parameter settings. This is a much lower rate than that reported by Kartha *et al.* (1975) where the corresponding figure is about 1 in 50 parameter settings on a sample of similar size. It should be noted however that the latter appears to be based on a retrospective analysis. It should also be noted that our earlier results obtained in 1973 (Rosenbloom and Bentley, 1976) on a very small sample showed seven errors in 193 set-ups which is equivalent to about 1 in 80 parameter settings, much closer to Kartha's figure.

Future development

At present we are checking only the machine parameters without any reference to the position of the patient. The data read out system for the SL75 includes parameters of couch position but they are not used because these contribute little to the measurement of patient position. We are now in a position to measure couch height and hope also to incorporate an optical device, developed from the work of Lillicrap and Milan (1975), to measure the FSD in a later version of the system.

It has been demonstrated by Sutherland (1973) that errors are made in prescriptive calculations and in dose recording. His results have been obtained by systematic retrospective checking, keeping detailed records of every error detected. At the Royal Marsden Hospital, similar checks are made by the radiographers but they do not keep statistics of the errors that they find. As an aid in this checking and to help the radiographers more generally, we are now concentrating on using the computer to produce duplicate record sheets automatically.

The present work has provided some preliminary results on error rates in setting up treatments for radiotherapy. In the near future, all patients treated on one linear accelerator will be monitored. The system should continue to prevent mistakes and provide a larger sample for analysis, with the automatic production of duplicate patient record sheets leading to improved use of the radiographers' time and skills.

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A model for treating post-irradiation nausea and vomiting in man: the action of insulin in abolishing radiation-induced delay in gastric emptying in the rat

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ABSTRACT

Radiation-induced delay in gastric emptying in rats, which may be comparable to radiation-induced nausea and vomiting in man, can be successfully treated with insulin. Biphasic insulin, given in the appropriate dose for the radiation exposure, restored the rate of emptying to normal and was used instead of soluble insulin which made the stomach empty quicker than normal. Some of the evidence suggests that this effect of insulin is related to its action on carbohydrate metabolism, but there was no simple correlation between the hypoglycaemic action of insulin and its effect on stomach emptying. A complete explanation for this action of insulin cannot be given at this stage but the possible involvement of intestinal hormones, such as enteroglucagon is discussed.

It is suggested that the use of insulin to treat radiation-induced nausea and vomiting in man should be considered.

The use of an animal experimental model for studying abnormalities of gastric function after irradiation has a number of advantages. A healthy individual is irradiated rather than one who may be ill or already suffering from symptoms associated with the alimentary tract. Psychologically induced gastric abnormalities are avoided and the investigation can readily be randomized, doses varied and mock irradiations and treatments used. The rat, although it cannot vomit, is particularly suitable as an experimental animal because the delay in gastric emptying which follows exposure to ionizing radiation is readily measured, is strongly dose-dependent and occurs after exposures as low as 20 R–50 R (Hulse, 1957; Fowler and Lawrey, 1960). The nausea and vomiting which may occur shortly after therapeutic exposure is also dose-dependent (Lushbaugh *et al.*, 1967) and examination of the limited data from radiation accidents tends to support such a relationship (Patricia Ash, personal communication). Experimental investigation of gastric dysfunction in species able to vomit has concentrated on the neurophysiological mechanisms of the post-irradiation vomiting (Brizzee, 1956; Borison, 1957; Wang *et al.*, 1958) rather than the mode of action of the radiation.

Nausea, being purely subjective, cannot be studied in rats but the delay in gastric emptying produced by relatively low doses may well be comparable to it. When rats, which had been trained to feed themselves with a barium meal, were irradiated shortly after the meal they developed an aversion to a second barium meal which unirradiated control rats did not (Hulse and Mizon, 1967). Presumably the aversion resulted from radiation-induced sensations, which were related by the rat to the taste and/or smell of the barium meal.

By following gastric emptying in the part-body irradiated rat, it was found that the radiosensitive site was largely in the upper (cranial) half of the abdomen and more on the right side of the body than the left (Hulse, 1966). Also irradiation of a small part of the abdomen through a one inch lateral port delayed emptying only slightly less than whole-body irradiation. A recent clinical report that irradiation of patients above the umbilicus was followed by moderately severe nausea and vomiting whereas irradiation below the umbilicus produced few such side effects (Fitzpatrick and Rider, 1976), confirms the experimental finding that local irradiation of the upper abdomen triggers the response and supports the validity of the rat as a suitable experimental model.

Ways in which the gastric delay might have been modified have been studied. The radioprotector cysteamine (β-mercaptoethylamine) had no therapeutic effect on stomach emptying in rats (Hulse, 1958), nor did it relieve nausea and vomiting in radiotherapy patients (Court Brown, 1955). Similarly, pyridoxine was found to have no beneficial effect in the rat (Hulse, 1967), confirming comparable clinical investigations (Silverman *et al.*, 1956; Mattie *et al.*, 1967).

In the present paper we report what we believe to be the first successful treatment of post-irradiation gastric delay in the rat. Depending on the amount administered, insulin, given after whole-body exposure to X rays, can restore the normal rate of emptying. Its action is discussed in terms of concomitant changes in the plasma glucose concentration. It is suggested that insulin is worthy of a trial in controlling gastro-intestinal symptoms in radiotherapy patients.

Materials and Methods

Male albino rats aged between three and seven months were given a whole-body exposure to 250 kV X rays (HVL of 1.2 mm Cu) usually at 75 R/min but in one experiment at 575 R/min.

Assessment of gastric delay

The details of the technique, which entails giving a barium meal without forced feeding, have been described in previous publications (Hulse, 1957; 1966). A commercial barium meal preparation (Horlicks Shadow Meal) was usually used but for one series of experiments a barium meal with minimum absorbable carbohydrate was needed. Following trials for palatability, consistency and speed of stomach emptying in unirradiated rats the following was used: barium sulphate 2.5 g, a mucilage of tragacanth made as the BPC mucilage but with half the quantity of water and no chloroform flavouring 1.0 g, cellulose 1.0 g, olive oil 0.2 ml and 0.17% (w/v) saccharin solution 2.0 ml.

One litter of four rats was used at a time and each rat was allocated to a different radiation or treatment schedule using a system of randomization. After starving overnight the rats were given their barium meals, irradiated or mock-irradiated and immediately afterwards the first radiographs were taken. The injections of insulin or other substances were then given and dorso-ventral and left lateral radiographs taken at ½, 1, 1½, 2, 3, 4, 5, 6 and 7 hours after the irradiation.

Stomach emptying was assessed visually from the serial radiographs, six degrees of fullness being readily distinguished *viz.* 100%, 75%, 50%, 25%, 10% (trace) and empty. Mean scores for stomach fullness were calculated at the various times after irradiation.

Substances tested

Preliminary trials with soluble insulin indicated the need to use a more slowly acting preparation. Biphasic Insulin Injection, BP ("Rapitard", Novo) was chosen. This consists of crystals of bovine insulin in a solution of porcine insulin and combines the properties of a quick acting insulin with the medium duration action of the crystalline component. For practical reasons the preparation had to be diluted with isotonic saline immediately before use. The dilutions ranged from 1:4 to 1:200 and the amount injected from 0.05–1.0 ml, always given subcutaneously. When blood glucose was being measured, controls received 0.2 ml of isotonic saline by the same route. As it had been shown previously that a single subcutaneous injection of isotonic saline did not alter stomach emptying (Hulse, 1958) it was not considered necessary to inject control rats with saline when gastric delay was being measured.

The effect of glucagon on gastric emptying was tested by giving 1.0 mg (1.0 ml) of glucagon USP (Lilly) subcutaneously at hourly intervals for five hours (six doses). Controls were given the same volume of isotonic saline subcutaneously. In similar tests of glucose 1.0 ml of an isotonic solution (54 g/l) was given intraperitoneally for five hours (six doses) and control rats were given the same amount of saline at the same time intervals.

Plasma glucose estimation

Under sodium pentobarbitone anaesthesia, blood was quickly withdrawn from the abdominal aorta into a heparin-treated syringe. The plasma was separated at once by centrifugation and the proteins precipitated with 5% (w/v) $ZnSO_4$ and 0.3 N $Ba(OH)_2$. Glucose was estimated specifically in duplicate aliquots by the glucose oxidase method (Sigma Chem. Co. Tech. Bulletin 510, 1969). In one experiment total reducing sugars were also measured using the Nelson-Somogyi method (Varley, 1962).

Results

Soluble insulin

After 200 R of X rays the stomach rarely showed any evidence of emptying over the seven-hour period of observation (Fig. 1), confirming early observations (Hulse, 1966).

When a dose of 1.0 units (u) of soluble insulin was given immediately after the first post-irradiation radiograph the stomach started to empty straight away and continued to empty much faster than in unirradiated controls. However, after about three hours, the effect of the insulin appeared to cease. When the same dose of soluble insulin was given two hours after irradiation the response was similar.

Thus, soluble insulin could overcome radiation-induced gastric delay but, when compared with the pattern of emptying in control rats, the initial emptying was more rapid. Consequently biphasic insulin, which has a more gradual and prolonged action, was used in all subsequent experiments.

Biphasic insulin

Biphasic insulin, given immediately after the first post-irradiation radiograph, overcame radiation-induced gastric delay but without the precipitate emptying characteristic of soluble insulin. There was a systematic change in the degree of effect according

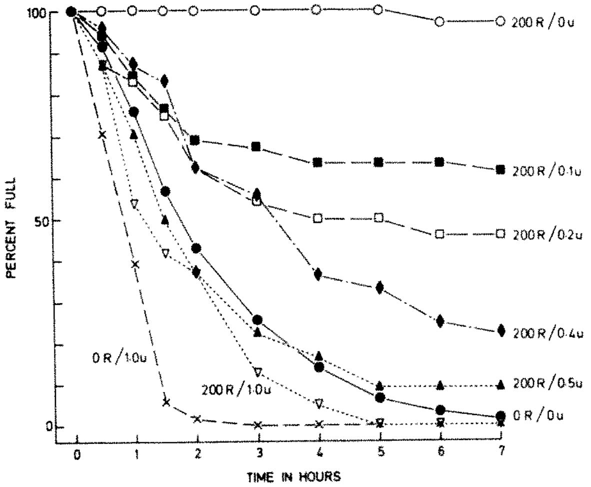

FIG. 1.

The effect on stomach emptying of various doses of biphasic insulin given immediately after 200 R of X rays. The mock irradiated were all litter mates of the irradiated rats. The curves are labelled thus: X-ray exposure (R)/dose of insulin (u). Each curve is derived from six rats except for mock-irradiated: 21 rats; 200 R/no insulin: nine rats and 200 R/0.1 u insulin: 13 rats.

to dose of insulin: observations after 200 R are shown in Fig. 1. After 0.5 u emptying was virtually the same as that in the unirradiated rats and with the larger dose of 1.0 u it was faster than that of the controls. Reduction of insulin dose to 0.4 u, 0.2 u and 0.1 u proportionally reduced the effect on the radiation-induced gastric delay but even after as little as 0.1 u a clear-cut response was obtained.

Two similar series of experiments were done using 600 R, which rarely kills acutely, and 1000 R, a lethal exposure which frequently causes diarrhoea and occasionally kills as early as five to seven days in this strain of rats. The patterns of response were similar to Fig. 1 but to achieve the same results larger doses of insulin were required, 2.5 u being needed to restore normal gastric emptying after 1000 R and 1.0 u after 600 R. Lesser doses were clearly insufficient and reducing the doses of insulin progressively reduced the effect on gastric delay.

A comparison of the degree of effect of different doses of biphasic insulin on the delay caused by the three doses of X rays, 200 R, 600 R and 1000 R, is given in Fig. 2. Means of the six- and seven-hour scores are used as a measure of the effects. Collecting the data together in this way clearly shows (i) that the higher the dose of insulin the greater the reduction in gastric delay and (ii) the higher the radiation exposure the greater the dose of insulin needed to achieve the same effect.

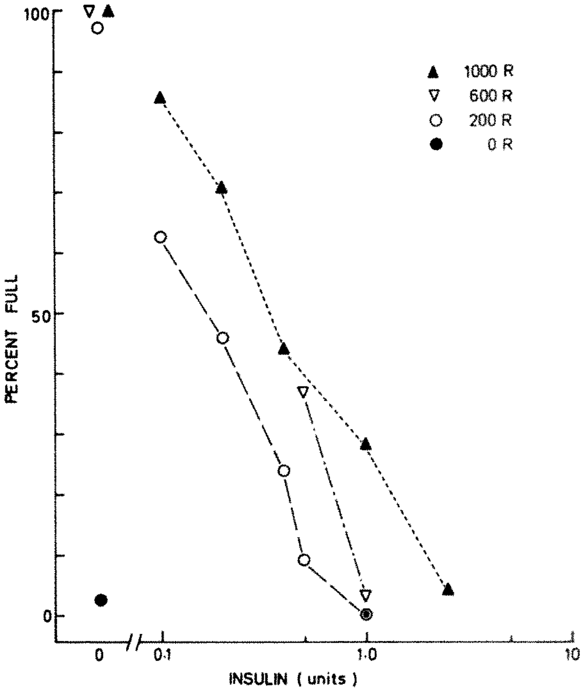

FIG. 2.

Stomach emptying of irradiated and mock irradiated rats related to dose of biphasic insulin (on a logarithmic scale), using the mean of six-hour and seven-hour scores as a measure of the effect.

TABLE I

CHANGES IN THE EFFECT OF INSULIN ON GASTRIC DELAY WHEN A BARIUM MEAL CONTAINING MINIMUM CARBOHYDRATE (MUCILAGE BARIUM MEAL) WAS USED INSTEAD OF ONE CONTAINING MALTED MILK (HORLICKS SHADOW MEAL)

(Means of 6–7 h scores)			
		Per cent fullness of stomach	
X rays (R)	Insulin (u)	Mucilage barium meal	Horlicks shadow meal
0	0	4	3
200	0	88	97
200	0.1	46	63

The effects of malted milk in the barium meal

As the insulin overcame gastric delay the barium meal entered the small intestine and, because the standard meal contained Horlicks Malted Milk, carbohydrates would presumably be absorbed. This possibility was avoided by using mucilage barium meal. The general pattern of response was similar to that using Horlicks Shadow Meal (Table I). The speed of emptying was no different in mock-irradiated rats though after 200 R emptying was perhaps a little faster with the mucilage barium meal. However, the effect of 0.1 u of insulin was greater with the mucilage barium meal than with the carbohydrate-containing barium meal.

Plasma glucose concentration

Preliminary experiments using unirradiated rats starved for 24 hours showed that plasma glucose was lower at two hours than at ½ hour or four hours after 0.1 u biphasic insulin, *i.e.* it was lowest at a time when insulin caused rapid gastric emptying (Fig. 1). Subsequently plasma glucose was measured at two hours in most of the experiments.

Rats were starved overnight, irradiated and then immediately injected with insulin, but not given barium meals lest absorbed carbohydrate interfered with the effects on plasma glucose. There was no consistent difference in the levels of plasma glucose between rats given 200 R and those given 1000 R (Fig. 3). The values were consistently higher in the irradiated than in the unirradiated rats after 0.05 u, 0.1 u and 0.2 u of insulin but not after 0.4 u. The rats which were not given insulin had a similar plasma glucose concentration whether irradiated or not (Fig. 3). This latter point was investigated further. After starving for 24 hours, groups of five rats were given 600 R and plasma glucose measured at two hours and six hours, others were given 2000 R or 5000 R (at 575 R/min) and both plasma glucose and total reducing sugars measured at two hours and four hours after irradiation. In no instance was the mean value for the irradiated rats significantly different from that of their mock-irradiated litter-mates.

In order to duplicate the conditions of gastric emptying experiments the effect of insulin on plasma glucose was tested on rats starved overnight, fed the standard barium meal, exposed to either 200 R or 1000 R and then injected with insulin. Compared with irradiated controls receiving no insulin, the magnitude of the reduction in plasma glucose depended on the X-ray exposure as well as on the dose of insulin: 0.1 u had less effect and 0.4 u more effect after 200 R than after 1000 R (Fig. 4). Given the interaction between radiation and insulin on stomach emptying (Fig. 2) and, presumably, on carbohydrate absorption, the unirradiated rats were not fed the barium meal, so making them more comparable to irradiated rats, particularly after low doses of insulin.

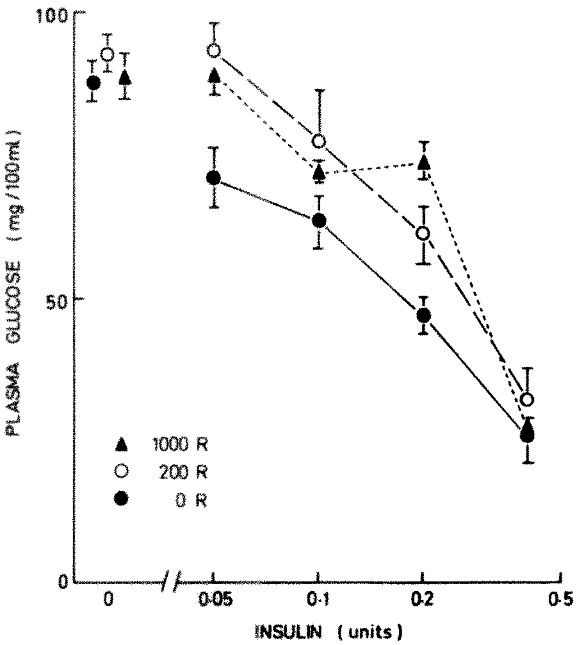

FIG. 3.

The effect on plasma glucose concentration of biphasic insulin and X-irradiation. Rats were starved overnight but not fed before irradiation or mock irradiation and plasma glucose was measured two hours after insulin injection. Means with S.E. for groups of four rats.

The effects of glucagon or glucose on gastric emptying (Table II)

Since insulin could overcome the gastric delay induced by radiation it seemed possible that insulin antagonists given to unirradiated rats might mimic the effects of radiation. A single dose of 1.0 mg of

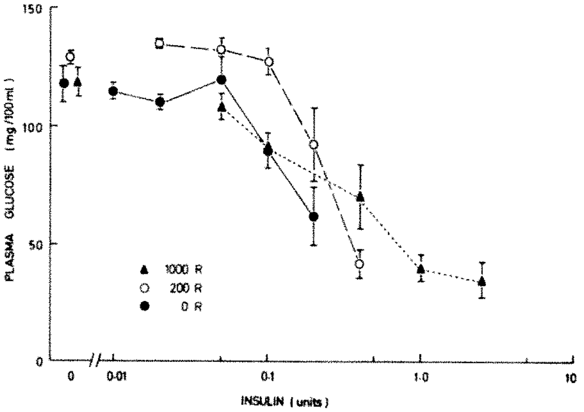

FIG. 4.

The effect on plasma glucose concentration of biphasic insulin and X-irradiation after feeding the barium meal containing Horlicks. The unirradiated rats were starved, as were the irradiated, but were not fed the barium meal. Means with S.E. for four to six rats.

TABLE II

GASTRIC DELAY INDUCED BY HOURLY INJECTIONS OF GLUCAGON OR GLUCOSE AND THE EFFECT OF INSULIN

Insulin (u)	Radiation (R)	Per cent fullness of stomach (means of 4–5 h scores)			
		Glucagon s.c.	Saline s.c.	Glucose i.p.	Saline i.p.
0	0	88	12	47	35
0.1	0	79	—	—	—
0.2	0	75	—	—	—
0.5	0	42	—	—	—
1.0	0	2	—	—	—
0.4	200	—	—	63	33

glucagon produced a transient delay in gastric emptying; in order to produce a sustained delay, comparable to that produced by X rays, hourly doses had to be given. Similarly, 1.0 ml of isotonic glucose had to be given hourly to produce a sustained delay. For our experiment, therefore, we gave either substance hourly for five hours: subsequently their effects wore off rapidly. Accordingly, in Table II the scores of stomach fullness are the mean of the four and five hour measurements and later observations at six and seven hours were not used.

The repeated injection of glucagon in unirradiated rats resulted in a marked gastric delay. The same volume of saline given subcutaneously did not have any appreciable effect. Biphasic insulin counteracted the glucagon-induced delay, the effect increasing as the dose of insulin was increased from 0.1 u to 0.2 u and 0.5 u. A dose of 1.0 u emptied the stomach faster than normal in spite of the repeated doses of glucagon.

In unirradiated rats glucose delayed gastric emptying. Comparable intraperitoneal injections of saline also delayed gastric emptying but to a lesser extent. In irradiated rats given insulin the difference was much greater, the administration of glucose so counteracting the effect of 0.4 u insulin that the four to five hour score was almost doubled.

DISCUSSION

The observations described here show that radiation-induced gastric delay in rats can be successfully treated with insulin. Soluble insulin acted too rapidly to reproduce normal emptying but biphasic insulin, given in the appropriate dose, can restore the rate of emptying of the stomach to normal (Fig. 1). The amount of insulin needed to achieve this increased with the dose of radiation, though as little as 0.1 u of insulin did promote emptying even after 1000 R (Fig. 2).

Relationship to carbohydrate metabolism

Some of the evidence suggested that this action of insulin was related to its effect on carbohydrate metabolism: (i) the enhancement of stomach emptying and the depression of plasma glucose concentrations were brought about by broadly similar doses of insulin (Figs. 2, 4); (ii) Glucagon produced a delay in gastric emptying which could be counteracted by insulin and a glucose load itself caused some delay (Table II); (iii) 0.1 u insulin promoted stomach emptying after 200 R to a greater extent when the barium meal did not contain carbohydrate (Table I), *i.e.* when stomach emptying could not lead to intestinal absorption of glucose. Thus, in starved rats exposed to 200 R, 0.1 u insulin tended to reduce the plasma glucose concentration (Fig. 3), whereas in rats fed the barium meal containing malted milk the same combination of radiation and insulin did not produce hypoglycaemia (Fig. 4), presumably because of absorbed glucose.

There is, however, no simple correlation between the hypoglycaemic action of insulin and its effect on stomach emptying. For instance, in rats fed the barium meal containing malted milk and exposed to 200 R, 0.1 u insulin partially restored gastric emptying (Fig. 1), but as mentioned did not lower the plasma glucose level in such animals (Fig. 4); 0.5 u of insulin completely restored the emptying rate, but certainly would lower plasma glucose. In contrast, after 1000 R, 0.1 u of insulin did lower the plasma glucose concentration (Fig. 4) but only slightly enhanced gastric emptying (Fig. 2); 2.5 u of insulin increased the emptying rate more than did 1.0 u (Fig. 2) but scarcely reduced the already low level of plasma glucose (Fig. 4). In starved rats insulin, at all dose levels tested, reduced the plasma glucose concentration approximately equally after 200 R and 1000 R (Fig. 3), but it is clear that after increasing doses of radiation more insulin was required to restore the normal rate of gastric emptying (Fig. 2).

In rats not given insulin we neither detected any increase in plasma glucose concentration after exposures of 1000 R (Fig. 3) or even 5000 R, nor was there any increase in other reducing sugars. There have been reports of raised levels of reducing sugars in the plasma of non-fasting rabbits (Thompson and Steadman, 1951) and non-fasting rats (Barkalaya, 1970) after exposure to 500 R and 750 R respectively. This increase could be prevented by the administration of insulin (Steadman and Grimaldi, 1952).

Possible mechanisms

No complete explanation can be offered at this stage for the action of insulin on the stomach, nor indeed for the inhibition of gastric emptying by radiation. We infer from part-body irradiation studies (Hulse, 1966) that the radiosensitive organ may be the proximal small intestine. Local concentrations in the duodenum of, among other metabolites, carbohydrates are known to play a part in the normal regulation of gastric emptying (Cooke, 1975). Those concentrations may conceivably be affected by radiation, because of cell killing in the intestine. Also, independently of radiation, gastric emptying may be affected by concentrations of glucose in the duodenal tissues as well as in the lumen, and so be sensitive to insulin.

Again, it is possible that an intestinal hormone such as enteroglucagon may be involved in radiation-induced delay, *e.g.* by local release following cellular damage. It has been suggested that the well known effect of glucagon on intestinal motility may be due to cross-reaction with enteroglucagon receptor sites (Bloom *et al.*, 1972), so enteroglucagon may be able to inhibit gastric emptying. Furthermore, injected insulin reduced the level of circulating enteroglucagon (Persson *et al.*, 1971). In a preliminary investigation into this hypothesis (Hulse, Patrick and Bloom, unpublished observations) starved rats were exposed to 0, 200 R or 1000 R of X rays and after two hours blood was taken for analysis by radioimmune assay (Bloom, 1972). Although the level of enteroglucagon did increase with increasing radiation dose, the effect was not statistically significant. The pancreatic glucagon level was not affected at all. Further work would be required to ascertain whether enteroglucagon, or any other intestinal hormone, is indeed involved in the actions of radiation and insulin on gastric motility.

Clinical implications

As already noted at the beginning of this paper, radiation-induced delay in gastric emptying in the rat may be analogous to radiation-induced nausea and vomiting in man. Thus the present findings suggest the possibility that insulin might be of use in controlling these symptoms. In practical terms it is worth underlining that in some circumstances, *e.g.* 0.1 u after 200 R, insulin could enhance gastric emptying without lowering plasma glucose (Figs. 1, 4). However, in all cases the dose of insulin needed to restore the normal rate of emptying lowered plasma glucose in the rat. As insulin is used therapeutically in anorexia nervosa and other psychological conditions information is already available on its use in the non-diabetic.

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Book review

Fairbanks, Atlas of General Affections of the Skeleton. By R. Wynne-Davies and T. J. Fairbank, pp. xiii+262, illus., 1976, (Churchill Livingstone, Edinburgh) 2nd edn., £22·00.

It is now 25 years since the first edition of this atlas by Sir Thomas Fairbanks appeared. The first edition soon established itself as a standard reference work in the difficult field of generalized skeletal disease. This long-awaited second edition is a worthy successor and will be welcomed by all.

The book is divided into six sections which group the diseases into bone dysplasias, miscellaneous dysplasias and malformations, inborn errors of metabolism, metabolic bone disease, endocrine disorders and a miscellaneous group of infections, toxins, blood dyscrasias, neoplasia and trauma. This, in association with a very full index, which includes not only the major diseases but specific radiographic signs and laboratory findings, enable the reader to reach rapidly the appropriate point in the book. In each section the disorders are presented in a logical order resulting in a list of contents which is also a useful classification. There is an additional table which lists the disorders in accordance with their typical age of presenting signs which may be at birth, in infancy, childhood, adolescence or adult life. Each disease entity is described under headings of inheritance, frequency, clinical and radiographic features, pathology, differential diagnosis, progress and complication. Most are accompanied by typical illustrations and there is a list of key references at the end of each account.

The book has been compiled by two orthopaedic surgeons and not surprisingly the descriptions of radiographic signs are rather superficial, the references are predominantly from the orthopaedic literature and there is scant mention of the radiological literature. The illustrations are generally of poor quality which belies the title of an atlas. There are a number of statements in the text with which some readers may take issue. Not all, for example, will agree that polyostotic fibrous dysplasia and idiopathic juvenile osteoporosis are extremely rare, or that biopsy may be necessary to distinguish between Paget's disease and sclerotic metastases in bone. The classification of Von Buchem's disease as a type of hyperphosphatasia is not generally accepted and is not justified by the variability in the level of serum phosphatase found in this disorder. The subjects of progeria, dyschondrosteosis and of monostotic fibrous dysplasia, might have been included with advantage.

Despite these minor criticisms, the book provides an excellent succinct account of the many conditions presenting with generalized skeletal abnormalities and will provide an excellent starting point in the study of this subject in general and of individual problem cases in particular. It should be available to all practising radiologists, be included in all radiological departmental libraries and will be equally valuable to clinicians, particularly paediatricians and orthopaedic surgeons. It is indeed an outstanding addition to the world literature.

J. ROYLANCE.

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RBE of neutrons generated by 50 MeV deuterons on beryllium for control of artificial pulmonary metastases of a mouse fibrosarcoma*

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ABSTRACT

Artificial pulmonary metastases of a mouse fibrosarcoma were produced by the intravenous injection of 10^4 cells admixed with 2×10^6 plastic microspheres into mice preconditioned with 600 rad whole-body irradiation 24 hours earlier. Four days after injection of tumour cells, mice were irradiated with neutrons generated by 50 MeV deuterons on Be at the Texas A & M Variable Energy Cyclotron or with ^{137}Cs γ rays. One, three or six fractions of radiation were delivered on a three-hour fractionation schedule. Surviving lung metastases were scored macroscopically 16 days after irradiation. The data indicate that: (1) the RBE (n/γ) was in the range 1.6–2.6 depending on the size of dose per fraction; (2) the slopes of the γ-ray curves decreased with increasing fraction number (*i.e.* decreasing fraction size); (3) the slopes of the neutron curves decreased only slightly with increasing fraction number (and decreasing fraction size); (4) no additional sparing was achieved by further fractionating doses of neutrons of 300 rad or less.

The aim of this investigation was two-fold: first to develop an *in vivo* system with which the radiobiological characteristics of artificial pulmonary metastases of an experimental rodent fibrosarcoma could be studied using clinically-relevant doses of radiation (100–400 rad per fraction); and second, to establish the relative biological effectiveness (RBE) of neutrons generated by 50 MeV deuterons on Be with respect to γ rays for control of this tumour using single and fractionated doses. RBE is defined as the inverse of the ratio of the dose of a test radiation to the dose of a reference standard radiation giving the same biological effects (Storer *et al.*, 1957).

MATERIALS AND METHODS

Mice and tumours

Female C_3Hf/Bu mice, 10–12 weeks old from the M. D. Anderson Hospital specific pathogen-free mouse colony, were used for all experiments. The mice were maintained on a sterilized pellet diet (Wayne Sterilizable Lab Bloc), sterile acidified water (pH 2.5), and a 12-hour light-dark cycle.

The tumour, a fibrosarcoma, was originally induced in a young female mouse by a single subcutaneous injection of 1 mg methylcholanthrene suspended in peanut oil (Suit and Suchato, 1967). Tumours of the fifth generation were used for all experiments.

The enzymatic (trypsin digestion) procedure for obtaining single cell suspensions was that described previously (Milas *et al.*, 1974). Briefly, non-necrotic tissue was minced and trypsinized for 20 minutes. The resulting digest was mixed with medium 199 (Difco Laboratories) containing 10% fetal calf serum (FCS). This suspension was passed through a stainless steel mesh (80 wires per cm) into 15 ml conical centrifuge tubes and centrifuged once at 1000 rpm and once at 700 rpm in a clinical benchtop centrifuge. The resulting cell pellet was resuspended in fresh medium 199 with 10% FCS. Cell viability as determined by phase contrast microscopy and exclusion of 0.25% trypan blue was routinely greater than 90%.

The desired number of tumour cells (10^4) was suspended in medium 199 with 10% FCS and mixed with 2×10^6 plastic microspheres with diameters of 15 ± 5 μm (Minnesota Mining and Manufacturing) to increase the cloning efficiency (Hill and Bush, 1969). The resulting suspension was injected into a lateral tail vein of whole-body irradiated recipient mice (see below). Untreated controls were sacrificed 14 days after injection of cells while treated animals were sacrificed 16 days after thoracic irradiation (see Results). The mice were sacrificed by cervical fracture. Lungs were removed, the five lobes separated and placed in Bouin's fixative for 24 hours. The colonies of tumour cells were seen as round white nodules on the surface of the yellowish lung. Colony counts were made with the naked eye.

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Animals used in this study were maintained in facilities approved by the American Association for Accreditation of Laboratory Animal Care, and in accordance with current United States Department of Agriculture and Department of Health, Education, and Welfare, National Institutes of Health regulations and standards.

Whole-body irradiation

All animals were preconditioned with 600 rad γ-radiation to the total body 24 hours prior to the intravenous (i.v.) injection of viable tumour cells, for two reasons: to increase the cloning efficiency of the tumour cells in the lungs (Withers and Milas, 1973), and to minimize bias caused by immune suppression associated with the technical requirement of irradiating the whole-body when treating artificial lung metastases with neutrons compared with irradiating the thorax only with γ rays. Groups of five animals were irradiated to the whole-body in a ^{137}Cs unit with a single source situated 28 cm from mid-mouse as described previously (Stone and Withers, 1975).

Irradiation of artificial pulmonary metastases

1. γ rays: Mice were irradiated locally to the thorax using a dual source ^{137}Cs unit. A similar unit has been described (Hranitzky *et al.*, 1973). The dose rate was 195 rad per minute, determined by lithium fluoride thermoluminescent dosimeters. The mice were held in position in a tubular Lucite jig with the thorax positioned in the 3 cm diameter field. The fractionation interval for all split dose experiments was three hours. Thoracic irradiations were performed four days after the i.v. injection of tumour cells into preconditioned mice.

2. Neutrons: The Texas A & M Variable Energy Cyclotron (TAMVEC) was used for all neutron irradiations. Neutrons were produced by bombarding a beryllium target with a beam of 50 MeV deuterons. Mice received whole-body irradiation at a dose rate of 90 rad per minute. Whole-body irradiation was given because of difficulties in collimating the neutron beam for local irradiation of the thorax. The mice were protected from haematopoietic death by bone marrow reconstitution (see below). Mid-line doses in rads were determined using a 0.1 cm^3 tissue-equivalent ion chamber inserted in a mouse phantom which was a $1.9 \times 1.9 \times 7.0$ cm block of Shonka A-150 tissue equivalent plastic (Shonka *et al.*, 1958). Groups of eight mice were positioned in individual well ventilated Lucite boxes on the front face of a 40 cm Lucite tank containing tissue-equivalent liquid (Frigerio *et al.*, 1972). The distance from target to mid-mouse was 141 cm. The average distance from the front face of the Lucite mouse holder to the surface of the lung was 5 mm. At 3 mm depth, the dose is 92% of maximum; at 4 mm, 98% of maximum; at 5 mm 99% of maximum (Almond *et al.*, 1973).

3. Comparison of irradiation techniques: Experiments were performed to determine if the techniques used for neutron irradiation to the whole body and γ irradiation to the thorax alone yield comparable results. Animals were given 600 rad of γ rays to the whole body 24 hours prior to the i.v. injection of 10^4 tumour cells and 2×10^6 plastic microspheres. Four days after injection, groups of eight animals were irradiated either whole-body or locally to the thorax with γ rays. The results in Table I show no difference between the two groups in the slopes of the survival curves, both values of D_0 being 127 rad. Although the difference in numbers of lung colonies was not significant at $p = 0.05$ it should be noted that the number of surviving colonies in whole-body irradiated mice tended to be higher. The effect of more colonies surviving in WBI mice would be to make the RBE for the neutrons slightly larger than that reported.

TABLE I

EFFECT OF IRRADIATION TECHNIQUE

γ-ray dose (rad)	Lung colonies Mean ± SEM	
	Whole-body irradiation	Local thoracic irradiation
750	10.5±1.6	6.9±0.9
900	5.6±1.5	4.5±0.8
1050	0.5±0.3	0.8±0.2
1200	0.6±0.3	0.1±0.1

No significant difference in the number of surviving FSA lung colonies was found at the doses assayed when compared using the student's *t* test. In addition, the slopes of the survival curves were not significantly different ($D_0 =$ 127 rad).

All mice exposed to neutrons were rescued from haematopoietic death by the i.v. injection of 5×10^6 viable bone marrow cells 24 hours after irradiation. For this purpose bone marrow from tibiae and femora of donor mice was expelled into a beaker by forcing medium 199 through a needle inserted into the marrow cavity. Viability, determined by phase contrast microscopy, was greater than 90%.

Analysis of results

The number of surviving clonogenic tumour cells was plotted as a function of radiation dose in rad on semilogarithmic coordinates. The curves were fitted to the data using a least squares regression analysis. Date were plotted as the mean±standard error of the mean (SEM). The results were statistically evaluated using student's *t* test.

RESULTS

The optimum time at which to sacrifice the animals after irradiation was determined on the basis of the size and number of lung nodules. It can be seen in Fig. 1 that in control animals which received 10^4 cells the maximum number of lung nodules was observed by 10–12 days after injection and thereafter they increased only in size. Day 14 was chosen as the optimum time to sacrifice control animals because lung nodules were most easily counted then. If the animals were irradiated to the thorax with 600 or 1000 rad of γ rays four days after injection of tumour cells, the nodule counts did not significantly change from 16 to 22 days after injection (Fig. 1). The nodule size in these mice was most like that in control animals when scored 20 days after injection, that is 16 days after irradiation. Lung colonies in neutron irradiated and γ-ray treated animals were of comparable size 16 days after irradiation.

Single and multifraction dose response of tumour cells to γ rays and neutrons generated by 50 MeV deuterons on Be

The single and multifraction dose response curves of the artificial pulmonary metastases are shown in Fig. 2. Each point represents the mean colony count from eight animals plotted with the SEM. The important features to be noted are:

1. The γ-ray curves show a progressive shift to the right to higher doses as the fraction number is increased. This reflects repair of sublethal damage between dose fractions (Elkind, 1967).
2. The RBE of neutrons is greater than 1 at all doses tested.
3. The slopes of the γ-ray curves decrease (and values for D_0 increase) with increasing fraction number, the result of decreasing size of dose per fraction (Table II). Since the slope of the survival curve obtained with multiple equal fractions reflects the slope of the single dose survival curve over the range of doses used in multifraction exposures (Withers *et al.*, 1975), the decreasing

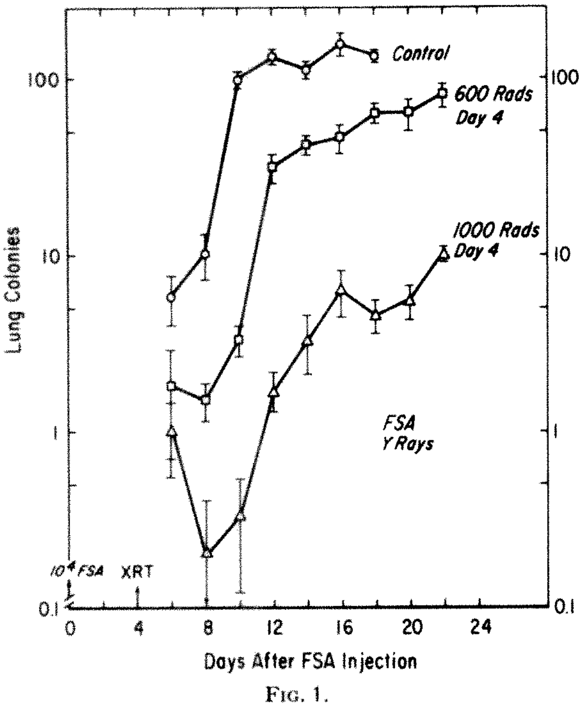

Fig. 1.

Number of macroscopic fibrosarcoma (FSA) lung colonies plotted as a function of time after injection in untreated controls and after irradiation with 600 or 1000 rad thoracic irradiation with γ rays. Thoracic irradiations were performed four days after i.v. challenge with 10^4 FSA cells admixed with 2×10^6 plastic microspheres. Data are plotted as the mean ± SEM.

TABLE II

D_0 values for 1, 3 and 6 fraction survival curves for artificial pulmonary metastases exposed to γ rays or neutrons

Fraction number	Range of doses per fraction	Slope D_0 (95% confidence limits)
γ rays		
1	700–1350	150 (124–189)
3	375–650	189 (171–210)
6	175–425	259 (232–292)
Neutrons		
1	300–700	101 (91–112)
3	180–310	119 (111–128)
6	80–160	115 (113–118)

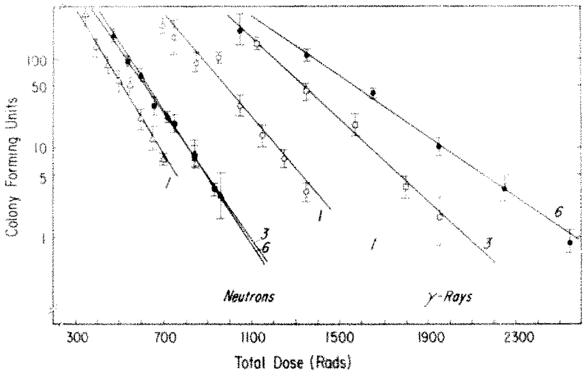

Fig. 2.

One, three and six fraction survival curves for pulmonary metastases exposed to neutrons or γ rays. Preconditioned (600 rad to whole-body) animals were irradiated four days after the i.v. injection of 10^4 cells admixed with 2×10^6 plastic microspheres. Animals were sacrificed 16 days after irradiation. Data are plotted as the mean ± SEM. Colony forming units are plotted as a function of radiation dose on semi-logarithmic coordinates.

slope of the γ-ray curves with decreasing fraction size reflects the shallower slope in the shoulder region of the single dose curve.

4. The slopes of the neutron curves decrease only slightly with decreasing fraction size (Table II). This is consistent with a single dose survival curve which is exponential over a wide dose range (at least from 80 to 300 rad). Changes in radiosensitivity of surviving cells related to the division cycle during the fractionated dose regimens could account for small differences in slope; this makes definite statements about survival curve shape impossible.
5. The three and six fraction neutron curves are superimposed on each other (Fig. 2). Thus, when doses per fraction are 300 rad or less, no additional sparing is achieved by further fractionation into lower doses per fraction. This implies that all cell killing from doses up to at least 300 rad results from "single-event", non-repairable injury.

RBE values derived from the survival curves in Fig. 2 are plotted as a function of γ-ray dose on linear coordinates in Fig. 3. On linear coordinates the curve bends, the RBE increasing as the dose per fraction is decreased. Plotted on logarithmic coordinates, RBE values may be fitted by a straight line (Fig. 4) over the dose range tested. Both graphs demonstrate that the RBE increases with decreasing size of dose per fraction. For example, at 200 rad of γ rays the RBE was 2.55, while at 1500 rad it was 1.70.

Discussion

The rationale for neutron therapy has been threefold. First, most solid animal tumours have been found to contain hypoxic cells (Barendsen and Broerse, 1969; Stone and Withers, 1975; Suit and Maeda, 1966). Neutrons have been found to be more effective, relative to γ rays, in damaging hypoxic cells (Barendsen and Broerse, 1966; Hall *et al.*, 1975). However, the importance is not that a tumour contains hypoxic cells, but that these cells may limit the curability of the tumour. It has been found in many tumours that a natural continuing process of reoxygenation occurs between dose fractions (Van Putten and Kallman, 1968). In this situation, neutrons lose some of their therapeutic advantage over γ rays. In the tumour model used in this study, it is unlikely that hypoxic cells, if present, significantly affect the radioresponse of this tumour as evidenced by the radiosensitivity of the cells to single doses of γ rays (D_0 150 rad) which is similar to that of most well oxygenated tissues, and by the low RBE values. At present, it cannot be predicted which tumours will remain sufficiently hypoxic during fractionated dose radiotherapy that they would respond better to neutrons than to conventional radiotherapy. A comparison of the responses of a variety of animal tumours to neutrons and γ rays may help to predict those types of tumours which could benefit from neutron therapy (Howlett *et al.*, 1975).

The second potential therapeutic advantage of neutrons is that their biological effect is influenced to a lesser extent than that of γ rays by progression of cells through the division cycle (Withers *et al.*, 1974b). Exploitation of this difference is difficult without detailed knowledge of the kinetics of both the tumour and the adjacent normal tissues. Therefore, this difference has not been systematically exploited and any advantages gained from this differential response has been strictly fortuitous.

A third potential advantage of neutron therapy is in reducing the variability in tumour response that may result if different tumours vary in their capacities for accumulating sublethal injury from γ ray exposure, that is, if tumour cells vary in the width of the shoulder of their survival curves. Once again, any

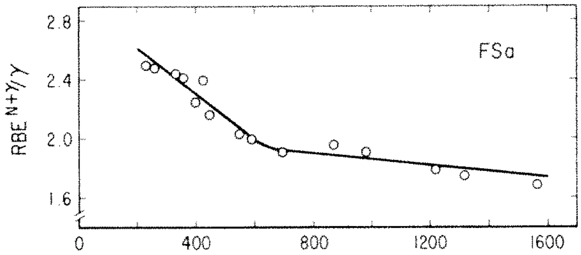

Fig. 3.

RBE values for neutrons and γ rays for control of artificial pulmonary metastases. RBE is plotted as a function of dose per fraction of γ rays on linear coordinates. The data are derived from the survival curves in Fig. 2. The RBE is the dose of ^{137}Cs γ rays divided by the total dose ($n+\gamma$) given when neutrons were used (50 MeV d on Be).

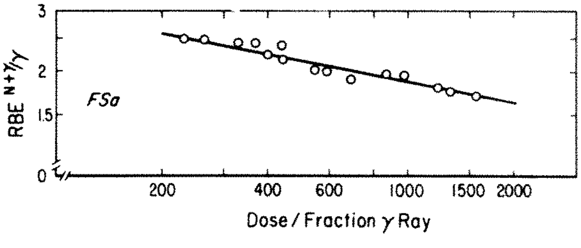

Fig. 4.

RBE plotted as a function of γ-ray dose on logarithmic coordinates.

advantage of using neutrons will require that the tumour be affected more than the normal tissue by eliminating the shoulder of the survival curve. The results presented in this paper suggest that the microscopic fibrosarcoma metastases would be relatively less affected by neutrons than would several normal tissues for which RBE values are greater than 2.5 at 200 rad of γ rays (Field, 1975).

The limiting factor determining the total dose delivered in radiotherapy is not the response of malignant tissue, but rather the acute and late normal tissue responses. In order for the RBE for tumour control to have any relevance, it must be compared with the RBE for effects on the normal tissues which are adjacent to the malignancy. Clearly, if the RBE for injury to the normal tissue is higher than for the malignant tissue, no therapeutic gain is achieved by using neutron therapy. In this situation, conventional radiotherapy would be the treatment of choice. Conversely, when the RBE is higher for the tumour than for the normal tissue around it, neutron therapy would be preferred. Table III presents RBE values at doses of about 180 rad of neutrons for some normal and malignant tissues exposed to neutrons generated at TAMVEC by 50 MeV deuterons on Be.

While it has been shown that the RBE of neutrons generated by 16 MeV deuterons on Be for producing lung damage is relatively low (Field, 1975), this RBE has not been determined for the higher energy neutrons at TAMVEC. If it were less than 2.25 at 180 rad of neutrons (*i.e.* less than the RBE for control of fibrosarcoma tumour cells at this dose), there would be a therapeutic advantage in treating these lung metastases with neutrons compared with photons. However, the limited total dose tolerance of the lungs to any form of irradiation would diminish the apparent attractiveness of neutron therapy in this experimental setting. In fact, the dose required to control these pulmonary metastases in 50% of the animals (~1600 rad) exceeds the LD_{100} for late respiratory death. It should be emphasized that the relatively low RBE values reported apply only to these small, presumably well oxygenated, tumours in the lungs. The RBE for control of tumours is likely to vary with tumour type, size, site of growth and oxygenation. Therefore, it is impossible to predict from these experiments whether neutron therapy would be advantageous in the clinical management of micrometastases in the lungs.

TABLE III

RBE values of some normal and malignant tissues irradiated at TAMVEC with neutrons generated by 50 MeV deuterons on Be

Tissue	Dose/ fraction of neutrons	RBE
Mouse artificial pulmonary metastases	180	2.25
Mouse jejunum (Withers *et al.*, 1974a)	190	2.5
Mouse testis (Withers *et al.*, 1976)	160	3.25
Melanoma, *in vitro* (Thomson *et al.*, 1975)	180	2.0
CHO, *in vitro* (Thomson *et al.*, 1975)	180	2.0
Rhesus monkey oropharyngeal damage (Jardine *et al.*, 1975)	180	2.4
Human mucosal reaction (Hussey *et al.*, 1974)	180	2.4
Pig skin contraction (Withers *et al.*, 1976)	180	2.55

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Book review

Ultrasonography of the Abdomen. By Nasser Hassani, pp. xvi+127, illus., 1976 (W. Germany, Springer-Verlag KG), $19.80.

Grey scale display has been available on commercial ultrasound equipment for over two years, but owing to the long delays in publishing medical books, there are still few books illustrating the value of this advance. There is thus a great need for an atlas of grey scale images of the abdomen, and this book attempts to fill that need.

The book boasts 215 illustrations and necessarily relies heavily on these illustrations with a basic minimum of text. However, 10% of the book is taken up by the two forewords, a preface, acknowledgments and an introduction. A further 25% is filled by a section on principles, machine controls (American equipment), administration of the department, duties of the technologist, etc. The first 35% is thus essentially redundant, the principles having now been covered in almost every book ever written on ultrasound.

This leaves only 90 pages of potentially useful text covering the non-obstetric uses of ultrasound and, given good quality illustrations, this could be most valuable. Regrettably, the scans included in this book are very poor. The basic ultrasound technique is frequently poor with excessive compounding, incorrect swept gain settings and no mention of the use of suspended inspiration for liver scanning. The grey scale of the original images is almost completely lost in these reproductions, most having only one shade of grey, some being positive, others negative, with no explanation of this in the captions.

Additionally, many pictures are laterally inverted, three with no mention of this in the text, two pictures are badly out of focus and two sets of legends transposed. The still images from a very dated "real time" scanner are very poor and serve no useful purpose.

The novice ultrasonographer will find the non-uniformity of image orientation and polarity confusing, the book of little value, and will have little difficulty in obtaining better images himself.

H. B. MEIRE.

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Some long-term effects of negative pions in mice exposed to partial body irradiation

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ABSTRACT

The long-term effects of partial body exposure of one-day-old mice given either ^{60}Co γ rays or negative pions have been studied. Both radiations produced considerable life-shortening; for pions $6.8 \pm 1.5\%$ of life is lost per 100 rad and for γ rays the value is $5.7 \pm 0.5\%$ per 100 rad. The RBE of pions for ten weeks of life-shortening is about 1.3 compared with ^{60}Co γ rays, although at lower doses the RBE may be higher reaching about two for six weeks of life-shortening. The incidence rate of tumours at any particular age was greater in mice irradiated with pions at the peak and in those given higher doses of γ rays than in the controls.

Negative pion beams of biologically significant intensity and momentum spread are now available and much of the recent work has been reviewed by Raju (1974). The 70 MeV pion beam at the Rutherford High Energy Laboratory, England, which delivers about 150 rad h^{-1}, has been used by a number of groups to study pion radiobiology. This work has recently been comprehensively reviewed by Ellis *et al.* (1976). In 1976 Coggle *et al.* reported on the induction of lens opacities in one-day-old mice given irradiation to the head and upper part of the body with either ^{60}Co γ rays at 1.5 rad min^{-1} or pions at 1 rad min^{-1}. These mice have now been systematically studied to determine both their life-span and the main causes of death and the results are given here.

MATERIALS AND METHODS

The pion beam from the proton cyclotron NIMROD is obtained from the interaction of a 7 GeV proton beam with a copper or tungsten target. The pions produced are focused along a 6 m beam and brought to the shielded experimental room. Ionization measurements show a peak to plateau dose ratio of 1.6 for particles of 160 MeV/c with a mean momentum spread of 15%. The current beam line using a tungsten target gives a dose rate of 150 rad h^{-1} over a volume of $2.5 \times 2.5 \times 3$ cm^3 at the 80% isodose contour. The electron, muon and neutron contamination of the beam is reasonably small. Muons contribute about 1% of the total peak ionization and are of low LET. Low LET electrons contribute about 5% of the total ionization at the pion peak. High LET neutron contamination is reduced by shielding and contributes less than 1% of the dose at the peak (Ellis *et al.*, 1976). The absorption of pions in tissue is the result of nuclear interactions with carbon, nitrogen and oxygen causing nuclear disintegration with the release of neutrons and "stars" of protons, alpha particles and heavy recoils which are locally absorbed. The LET distribution in the plateau is lower than in the peak region because of the smaller contribution from stars produced by pions interacting in flight. In the peak, pion stars contribute about 50% of the dose; based on calculations of Alsmiller *et al.* (1974) 25% of the peak dose is due to particles with LET greater than 10 KeV μm^{-1} and 10% from those greater than 100 KeV μm^{-1}. In contrast, in the plateau these high LET contributions are reduced by a factor of five.

Prior to all mouse irradiations a depth dose curve of the pion beam was determined and the position of the Bragg peak scanned in both vertical and horizontal planes to facilitate positioning of the mice. Since the irradiations, which took place in 1973/74, were designed to study the induction of lens opacities, and since the field size at the 80% isodose was only 2.5×2.5 cm^2, it was decided to irradiate only the head and upper part of the body of one-day-old mice. This enabled eight mice to be irradiated simultaneously, four in the plateau and four in the peak region of the beam. The mice were restrained in ventilated Perspex containers and arranged so that their heads were within the $2.5 \times 2.5 \times 3$ cm^3 irradiation volume. The containers were placed in a $10 \times 10 \times 18$ cm^3 Perspex phantom at the depths required for plateau and peak irradiation. The pion dose rate was about 1 rad min^{-1}. For comparison, groups of four one-day-old mice were placed in ventilated Perspex containers and positioned 2 m from a ^{60}Co γ-ray source. Their heads were directly in the beam and irradiated at 1.5 rad min^{-1}, whilst their bodies were shielded by lead wedges designed to reproduce the field size and distribution of the pion beam. The dose to the body was not more than 10% of that to the head. The doses and numbers of mice used are given in Table I.

All mice were caged under identical conditions, fed MRC diet 41B and given water *ad lib.* They were

TABLE I

RADIATION SCHEME FOR DAY-OLD MICE (EQUAL NUMBERS OF MALES AND FEMALES)

^{60}C γ rays		Pions	
Dose (rad)	No. of mice	Dose (rad)	No. of mice
0	120	0	160
40	48	40 (plateau)	60
60	48	60 (peak)	60
100	48	136 (plateau)	60
200	60	200 (peak)	60
300	60		

TABLE II

AGES AT WHICH MICE OF BOTH SEXES REACH 50% SURVIVAL (MEDIAN AGE)

Dose (rad)	Median age (weeks)	Standard deviation	Standard error	No. of mice
^{60}Co γ rays				
0	111.5	24.9	2.1	120
40	107.3	22.8	3.4	48
60	106.5	24.5	3.6	48
100	102.0	20.8	3.1	48
200	97.6	22.3	3.0	59
300	92.5	23.0	3.0	60
Pions				
0	110.9	23.0	2.1	146
40 (plateau)	105.5	21.3	3.0	54
60 (peak)	102.1	17.6	2.3	60
136 (plateau)	99.8	27.5	3.8	54
200 (peak)	95.8	25.3	3.8	46

examined daily for deaths or signs of morbidity, moribund mice being killed before death. A full post mortem on each mouse gave data on gross pathological lesions, many samples being studied histopathologically. This enabled a probable cause of death to be ascribed to 80% of the mice. However, difficulty remained in mice that were eaten, autolysed or which showed no significant pathological changes. The classification of pathological findings used in this study follows that of Lindop and Rotblat (1961b).

RESULTS

The age at death of every mouse was recorded and the percentage survival plotted against age in weekly intervals for each dose group. The difference between the sexes was so small that the analysis of life-shortening has been made for both sexes combined. Figure 1 shows the survival curves for control mice and those given 60 rad and 200 rad of pions at the peak to the head region alone. Figure 2 shows similar curves for controls and those given 60 rad and 300 rad of ^{60}Co γ irradiation. As can be seen the effect of such irradiations is to shift the survival curves towards a younger age. For the sake of clarity the survival curves for the other dose groups are not included in Figs. 1 and 2.

The amount of life-shortening for a given dose can be determined by comparing the ages at which mice, from different dose groups, reach a given percentage survival. Table II lists the median age (age for 50% survival) for mice of both sexes as a function of dose together with the standard deviation and error. The errors are obtained from a linear transformation of the survival curves. A plot of the probit of the percentage survival against age gave very good

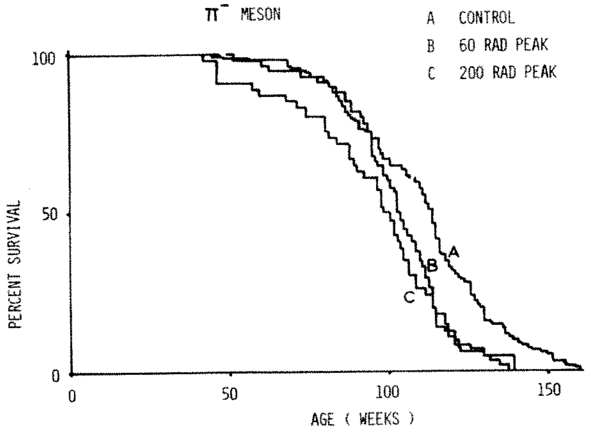

FIG. 1.

Survival curves of mice of both sexes for controls and mice given 60 and 200 rad of peak pions, at the peak at 1 rad min^{-1} to the head region only.

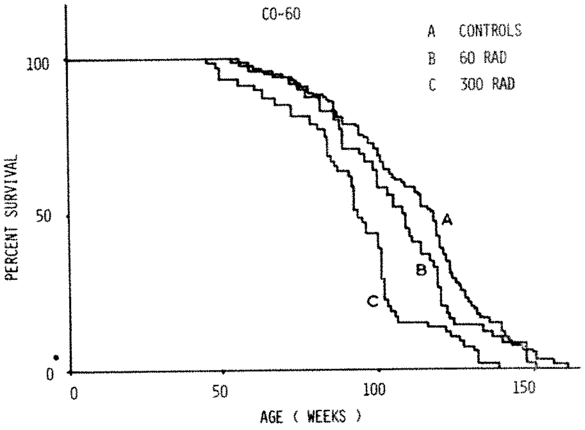

FIG. 2.

Survival curves of mice of both sexes for controls and mice given 60 and 300 rad of ^{60}Co at 1.5 rad min^{-1} to the head region only.

straight lines, six of the 11 lines having coefficients of correlations greater than 0.99, four with coefficients greater than 0.98 and one with a coefficient of 0.975. The derivation of confidence limits from statistical analysis of life-shortening is described by Lindop and Rotblat (1961a). Figures 3 and 4 are obtained from data in Table II and show life-shortening in weeks as a function of dose for pion and ^{60}Co γ irradiation respectively. The attempt to fit a straight line by regression analysis to the pion data (Fig. 3) proved rather unsatisfactory, with a coefficient of correlation of 0.93. In contrast, the ^{60}Co data (Fig. 4) fit a straight line very well with a coefficient of 0.99 and an intersection at the origin of 0.9 ± 0.7 weeks, showing that there is probably no threshold for life-shortening in young mice. In Fig. 3 the dotted line, drawn by eye through the pion points, curves steeply from the origin suggesting a greater relative effectiveness compared with γ rays at low doses. For example, the relative biological effect of pions for six weeks of life-shortening is about two compared with ^{60}Co γ rays. From the linear regression lines it can be calculated that for pions $6.83 \pm 1.51\%$ of life is lost per 100 rad and for ^{60}Co the value is $5.67 \pm 0.46\%$ life lost per 100 rad. The relative biological efficiency of pions for ten weeks life-shortening is 1.27 compared with ^{60}Co γ rays.

Table III gives the percentage of mice dying from various causes for each of the dose groups. The sex differences seen in the controls are generally maintained in the irradiated groups. Analysis also shows that at the doses used the percentage incidence of the causes of death did not really vary with dose, a finding in agreement with the much larger study of Lindop and Rotblat (1961b). However, the numbers of mice in the experiment (column 11) are too small to allow a meaningful analysis of mean age at death for each cause of death. However, by combining mice dying from all tumours (columns 1–5 in Table III) it is possible to analyse incidence rates of tumours using the methods of Peto (1974; 1976). Such an analysis shows that the incidence rate of tumours at any particular age is greater in the irradiated than in the control group for doses of 200 rad ($p=0.01$) and 60 rad ($p<0.05$) of pions at the peak, but not significantly different from controls for 40 and 136 rad of pions in the plateau. A similar analysis for the ^{60}Co data shows that the incidence rate of tumours at any particular age is greater in the 300 rad ($p<0.005$) and 200 rad ($p<0.005$) groups, but not significantly different from controls for 40, 60 and 100 rad. Since the irradiation was confined to the head and the upper part of the body, particular attention was paid to the brain but only six pituitary tumours were observed, four in the 266 controls and two in 475 irradiated mice.

DISCUSSION

Reported values for life-shortening in adult mice given whole body doses of X or γ rays vary between 3.3 and 7.8% life lost per 100 rad (van Cleave, 1968). The very large studies of Upton *et al.* (1960) and Lindop and Rotblat (1961a) gave values of 5.4–6.3% life lost per 100 rad. The values obtained in this

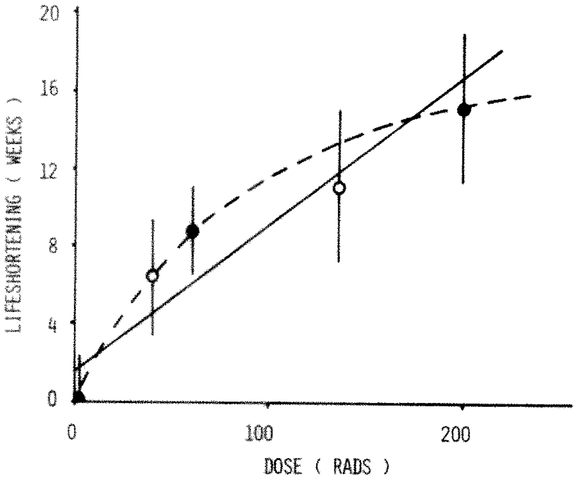

FIG. 3.

Life-shortening as a function of dose for mice of both sexes given pion irradiation. ● Peak pions; ○ Plateau pions.

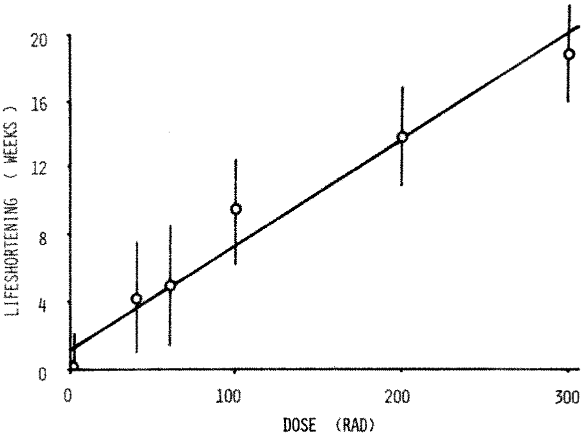

FIG. 4.

Life-shortening as a function of dose for mice of both sexes given ^{60}Co γ irradiation.

TABLE III

PERCENTAGE INCIDENCE OF DEATH FROM VARIOUS CAUSES

Dose (rad)	1 Leukaemia		2 Pulmonary tumours		3 Liver tumours		4 Ovarian tumours		5 Other tumours		6 Pulmonary		7 Renal		8 Liver		9 Intestinal		10 N.A.D.*		11 Total no.	
Pions	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0	8.3	14.9	18.1	18.9	5.6	4.1	—	4.1	8.3	13.2	15.3	5.4	9.7	4.1	4.2	2.7	19.4	16.2	11.1	13.5	72	74
40 (pl)	3.6	7.7	17.9	19.2	3.6	—	—	7.7	7.1	7.7	21.4	15.4	10.7	7.7	7.1	11.5	14.3	11.5	14.3	11.5	28	26
60 (pk)	6.7	10.0	23.3	10.0	10.0	—	—	13.3	10.0	10.0	16.7	20.0	—	3.3	6.7	3.3	20.0	13.3	6.7	16.7	30	30
136 (pl)	4.2	10.0	8.3	13.3	4.2	—	—	6.7	8.3	20.0	16.6	13.3	4.2	3.3	4.2	10.0	25.0	6.7	25.0	16.7	24	30
200 (pk)	3.6	5.6	25.0	5.6	3.6	—	—	22.2	7.1	22.2	10.7	11.1	14.3	—	—	5.6	17.9	11.1	17.9	16.7	28	18
^{60}Co γ rays 0	4.9	6.8	23.0	20.3	1.6	—	—	11.9	11.5	15.3	9.8	3.4	6.6	5.1	—	5.1	24.6	20.3	18.0	11.9	61	60
40	8.3	4.2	16.7	8.3	8.3	—	—	12.5	8.3	20.8	16.7	12.5	4.2	—	—	4.2	12.5	20.8	25.0	16.7	24	24
60	8.3	—	12.5	16.7	4.2	—	—	16.7	8.3	4.2	25.0	25.0	8.3	8.3	—	4.2	8.3	8.3	25.0	16.7	24	24
100	—	8.3	12.5	12.5	8.3	4.2	—	12.5	8.3	8.3	16.7	20.8	12.5	—	4.2	8.3	16.7	8.3	20.8	16.7	24	24
200	10.0	6.9	3.3	10.3	6.7	3.4	—	13.8	16.7	6.9	16.7	20.7	10.0	—	—	6.9	16.7	10.3	20.0	20.7	30	29
300	6.7	13.3	13.3	6.7	6.7	3.3	—	16.7	13.3	—	13.3	16.7	6.7	3.3	3.3	10.0	10.0	6.7	26.7	23.3	30	30

*N.A.D. = not any diagnosis.

study of 5.7% life lost per 100 rad of ^{60}Co γ rays and 6.1% per 100 rad of pions are in remarkable accord with published values considering the differences between this study and those in the literature. The values in the literature are for adult mice given whole body doses at dose rates greater than 50 rad min^{-1} whilst the one-day-old mice in this study received only rather low dose rate (1 rad min^{-1}) partial body exposure.

There appears to be a considerable decrease in the life-shortening effect throughout lifespan. Lindop (1965) noted that life-shortening per 100 rad varied from 6.7% for one-day-old mice to 1.3% for mice irradiated at an age corresponding to 70% of the lifespan of the controls. The data given in this paper on one-day-old mice showing higher sensitivity to life-shortening agree with the results of Lindop and Rotblat (1962).

Most reported life-shortening data are for dose rates of 25–100 rad min^{-1} and show no variation in effect between these rates; it seems that effectiveness falls only at chronic dose rates of less than 100 rad per day (Lindop, 1965).

The effect of partial body exposure on radiation life-shortening has not received any systematic attention. Most of the data in the literature are analogous to the present report and have been derived from experiments designed for other purposes. The few studies that have been done are reviewed by van Cleave (1968) who concludes that "partial body exposure of rodents is far less effective in shortening lifespan than whole body exposure". The findings of this paper are at odds with this conclusion, the irradiation of the head and upper parts of the thorax of one-day-old mice producing considerable life-shortening much of which is related to the induction of neoplasms. It is of interest to note that Sacher (1959) postulated that the potential longevity of a mammalian species depends to a significant degree on the size of its brain.

The initial reason for irradiating the mice was to compare the relative biological efficiency of pions with ^{60}Co γ rays, and from the fitted lines in Figs. 3 and 4 it can be calculated that pions are about 1.3 times more effective than ^{60}Co γ rays at reducing the lifespan of one-day-old mice by ten weeks. The dotted line drawn through the pion points in Fig. 3 suggest a higher RBE at low doses. Although this conclusion might be expected for the high LET pion radiation it is probably unwarranted from such a small number of points. The analysis of the incidence rate of tumours at any particular age was shown to be significantly greater for pions at the peak but not for pions in the plateau, which might be due to the higher LET components in the peak. The rather low RBE for pions is in agreement with the RBE of about one for the induction of macroscopic lens opacities found at 12 months post irradiation in these same mice and with several other *in vivo* end-points in mice (Coggle *et al.*, 1976), and for bone marrow stem cell survival reported by Carlson and Thornton (1976) and for testis weight loss (Coggle *et al.*, 1977; Gomez *et al.*, 1977). At present there is no adequate explanation of why the RBE for pions in *in vivo* systems in mice tends to be lower than RBE's reported for pions from the Rutherford High Energy Laboratory for *vicia faba* root growth (Winston *et al.*, 1973); cell survival *in vitro* (Nias *et al.*, 1974; Mill *et al.*, 1976); and chromosome aberrations in human lymphocytes (Lloyd *et al.*, 1975), all of whom reported RBE values of about two for pions at the peak.

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Technical notes

Rapid assay of unbound $^{99}Tc^m$ in preparations of $^{99}Tc^m$ labelled red blood cells

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Several recent articles on labelling of red blood cells with $^{99}Tc^m$ (Ducassou *et al.*, 1976; Smith and Richards, 1976) have reported labelling efficiencies without reference to the method or methods by which these yields were obtained. It has been shown (Dewanjee, 1974) that the $^{99}Tc^m$ which is strongly bound to the red blood cells (RBC) is associated with the haemoglobin, but the intrinsic membrane protein and sialoglycoprotein and the traces of plasma proteins which adhere non-specifically to the cell surface could also react with $^{99}Tc^m$ in the presence of tin (Sn^{+2}). These latter potential reactants probably represent $^{99}Tc^m$ that is weakly bound to the RBC. In addition, unreacted $^{99}Tc^m$ (VII) or colloid-reduced and hydrolyzed $^{99}Tc^m$ could also be presented in the reaction mixture. Instant thin-layer chromatography (ITLC), paper chromatography (PC) or the centrifuge assay system could be adapted to give estimates of the degree of dissociation of $^{99}Tc^m$ from the RBC but all these methods have disadvantages because of the nature of the labelled preparation. An ITLC or PC system, using an alcoholic solvent, would tend to overstate the labelling yield because only $^{99}Tc^mO_4^-$ would be detected and quantitated. The centrifuge assay requires a five to ten-minute centrifugation and one or two washes to effect complete separation of unbound $^{99}Tc^m$ from that bound to cells; in this case the labelling yield could be understated because excessive cell washings could induce lysis and/or leakage of label from the cell.

Therefore, we would like to present a microcentrifugation assay for $^{99}Tc^m$ RBC that requires only a 15 to 60-second centrifugation step with the entire assay procedure being completed in two to three minutes. The method uses a hydrophobic centrifugation medium composed of a 10:3 mixture of di-n-butyl phthalate and corn oil. There is complete separation of the particulate and liquid phases with the labelled RBC being pelleted and the hydrophilic substances being retained as a discrete supernatant phase. Loosely bound $^{99}Tc^m$ should be stripped from the cell surface by the hydrophobic medium thus providing a rapid index of RBC labelling efficiency. The yields obtained from the rapid microcentrifugation technique and the standard centrifugation assay were found to be comparable.

MATERIALS AND METHODS

Mouse RBC were labelled using a modification of the method of Eckelman (Eckelman *et al.*, 1971). Briefly, 1·0 ml of mouse blood was collected into acid citrate dextrose solution, centrifuged at 400 g for ten minutes at 4°C and washed twice with saline. The cells were incubated with 0·4 mCi of $^{99}Tc^mO_4^-$ for 30 minutes at 37°C and then 30 μl of 1 mg/ml $SnCl_2.2H_2O$ in acid citrate dextrose was added. The mixture was gently agitated for 15 minutes at 37°C, washed twice with saline and then resuspended in saline to give a final RBC count of $2–4 \times 10^6$ cells/mm^3.

Labelling efficiency was determined by PC using Whatman no. 4 paper and 70% methanol. A centrifugation assay was carried out by layering 0.1 ml of $^{99}Tc^m$-RBC onto 1.0 ml of a 10% sucrose solution and centrifuging at 1700 rpm at 4°C for ten minutes. The supernatant was collected and the cells were washed with 1.0 ml of 10% sucrose. The pellet and the two supernatants were assayed for radioactivity (Searle 1197) and the percentage of $^{99}Tc^m$ dissociated from the RBC was calculated.

For the microcentrifuge assay, 0.1 ml of a 10:3 mixture by volume of di-n-butyl phthalate (Fisher Scientific) and corn oil (Mazola) was loaded into 0.4 ml microcentrifuge tubes (Beckman) using a syringe and a long needle. Over this mixture was gently layered 0.05 to 0.10 ml of $^{99}Tc^m$-RBC. The suspension was centrifuged at 37°C for 15 to 60 seconds at 12–13000 rpm in a microcentrifuge (Beckman, model 152). The centrifuge tubes were cut with a razor blade just above the visible RBC pellet. The pellet, which adheres to the razor blade, can be scraped into a counting vial while the supernatant remaining in the body of the centrifuge tube is placed into another counting vial. The portions

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TABLE I

	Standard		Micro-		
	Centrifuge No wash	Assay 1 wash	Centrifuge 0.1 ml RBC	Assay 0.05 ml RBC	Paper chromatography* in 70% methanol
Batch 1 % unbound ^{99}Tc^{m}	8.1 ± 0.3	11.9 ± 1.4	10.9 ± 0.7	10.9 ± 0.6	4.0 ± 0.0
replicates	4	4	11	4	3
Batch 2 % unbound ^{99}Tc^{m}	14.1 ± 0.02	18.0 ± 0.3	17.3 ± 1.7	—	5.0 ± 0.01
replicates	4	4	6		3

*measures ^{99}Tc^{m}O$_4^-$ only.

can then be assayed for radioactivity and the per cent of ^{99}Tc^{m} dissociated from the ^{99}Tc^{m}-RBC calculated by dividing the radioactivity in the supernatant by the sum of pellet and the supernatant. The entire assay procedure can be completed in two to three minutes.

The results from the microcentrifuge assay, standard centrifuge assay and PC are shown in Table I. The microcentrifuge assay gives results which are comparable to those obtained from the standard assay with a single washing procedure. The PC procedures gives ^{99}Tc^{m}-RBC yields which are higher than those obtained from the two centrifuge assays, as would be expected if ^{99}Tc^{m}-labelled proteins and reduced ^{99}Tc^{m} in colloidal form were present in the reaction suspension.

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Method to quantify uptake of radiophosphorus in therapy of metastatic bone disease using ^{99}Tc^{m} radiophosphate

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Since the selective uptake of radioactive phosphorus (^{32}P) in neoplastic tissue was first described (Kenney *et al.*, 1941), numerous attempts have been made to enhance radiophosphorus uptake in metastatic bone disease, including prior administration of male hormones (Hertz, 1950), parathormone (Tong and Finkelstein, 1973), incorporation of radiophosphorus into long chain phosphates (Kaplan *et al.*, 1960) or into diphosphonates (Hall *et al.*, 1975). The results of treatment (Maxfield *et al.*, 1958; Parsons, 1961; Kaplan *et al.*, 1960), have been variable and unpredictable. We feel that this variability may be due, at least in part, to difficulties in estimating radiophosphate uptake, as external quantitation of the beta emission is impractical and reported dosage régimes have necessarily been empirical. It would be of advantage if a gamma emitting tracer which can be measured externally were associated with the radiophosphorus so that quantitation of ^{32}P uptake would become possible. It has been the object of this investigation to produce a radiophosphate coupled to such a gamma emitting tracer ^{99}Tc^{m}, and to investigate its suitability, using experimental animals, for this mode of therapy.

EXPERIMENTAL METHOD

^{32}P-sodium phosphate obtained as a trisodium phosphate solution was reduced to dihydrogen phosphate with HCl then fused at about 800°C producing a glassy mixture of long chain phosphates. Hydrolysis of this material at pH9 left a mixture of shorter chain phosphates with mean chain length

2·3 units. Minimal monophosphate was detected in the material using the method of Jones (1942). This phosphate mixture was found to form a stable stannous-technetium complex, a molar ratio of stannous chloride to phosphate of 3 to 1 ensuring virtually 100% binding of ^{99}Tc^{m}.

Localization was initially determined in the rat, assay of the ^{99}Tc^{m} tracer being determined by conventional gamma spectrometry, that of ^{32}P by Cerenkov counting of digested tissue samples and by autoradiography on sections. A healing tibial fracture in the rat was used as a tumour model, uptake within the ensuing area of increased osteoblastic activity being compared with a corresponding region in the opposite limb. Later a cat with an osteogenic sarcoma of the tibia was investigated.

RESULTS

As may be noted from Fig. 1, the uptake of ^{32}P and ^{99}Tc^{m} in bone were similar, and minimal clearance of either radionuclide was evident suggesting stable deposition within the bone matrix. Maximum uptake occurred within the active osteogenic region around the fractures, local uptake being from eight to 12 times that of samples of normal bone. A similar study using monophosphate showed much lower uptakes in bone (typically 20% to 30% of the synthesized phosphate uptake), as illustrated in the comparative autoradiographs of similar fractures in Fig. 2. The uptake of monophosphate was greater than that of synthesized phosphate in muscle and liver but less in kidney, and clearance of monophosphate from these organs proved slower.

The incorporation of tracer within an osteogenic sarcoma in a cat, Fig. 3, showed similarly increased uptake of both ^{99}Tc^{m} and ^{32}P within the sarcoma, some nine to ten times that of normal bone.

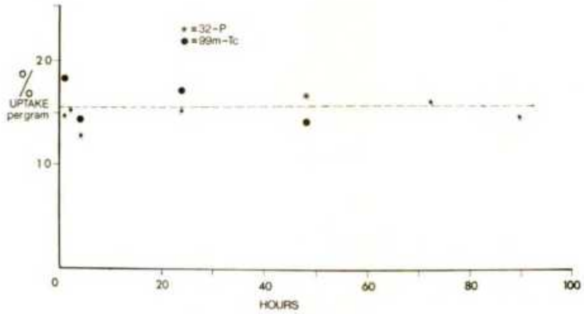

FIG. 1.

Clearance from rat bone of ^{99}Tc^{m} compared with ^{32}P after injection of ^{99}Tc^{m} and ^{32}P labelled condensed phosphate. Dotted line indicates mean uptake value.

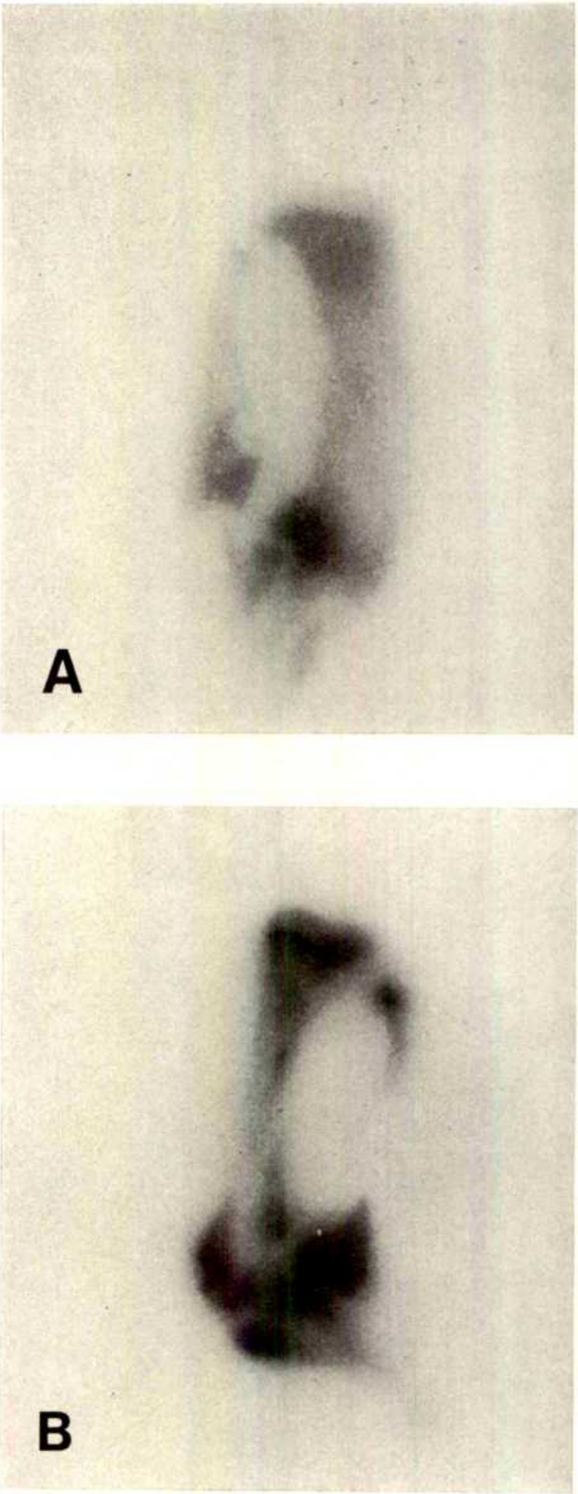

FIG. 2.

Autographs of healing rat tibial fractures using ^{32}P-sodium monophosphate (A) and ^{32}P-condensed phosphate (B).

DISCUSSION

The results after the empirical treatment régimes of metastatic bone disease with ^{32}P as hitherto employed showed periods of pain relief after treatment ranging from nil to 18 months. This variability may be partly because, using these methods, radiation doses cannot be estimated prior to treatment. Nevertheless it remains attractive in the management of wide-spread bone disease, when external radiotherapy and hormonal manipulation become ineffective, to consider the use of radiophosphorus which, if concentrated in scattered foci of tumour, would produce an intense local radiation effect from its energetic beta emission.

The animal experiments described indicate that the gamma emitting nuclide, ^{99}Tc^{m}, may be used to predict the uptake of radiophosphate in bone using external detectors. This means that quantitation in skeletal lesions and other organs may be attempted prior to therapy by using a tracer dose of the material, the suitability for therapy and therapeutic dosage being determined by the tracer dose uptake in a similar manner to that employed in thyroid therapy with radioiodine. In view of the retention in bone of the radiophosphate demonstrated in these experiments there would seem to be little point in the daily administration of the radiopharmaceutical recommended in earlier reports, longer intervals between injections being more appropriate. It is hoped that this study could provide a more rational approach to the radiotherapy of metastatic bone disease with radiophosphorus.

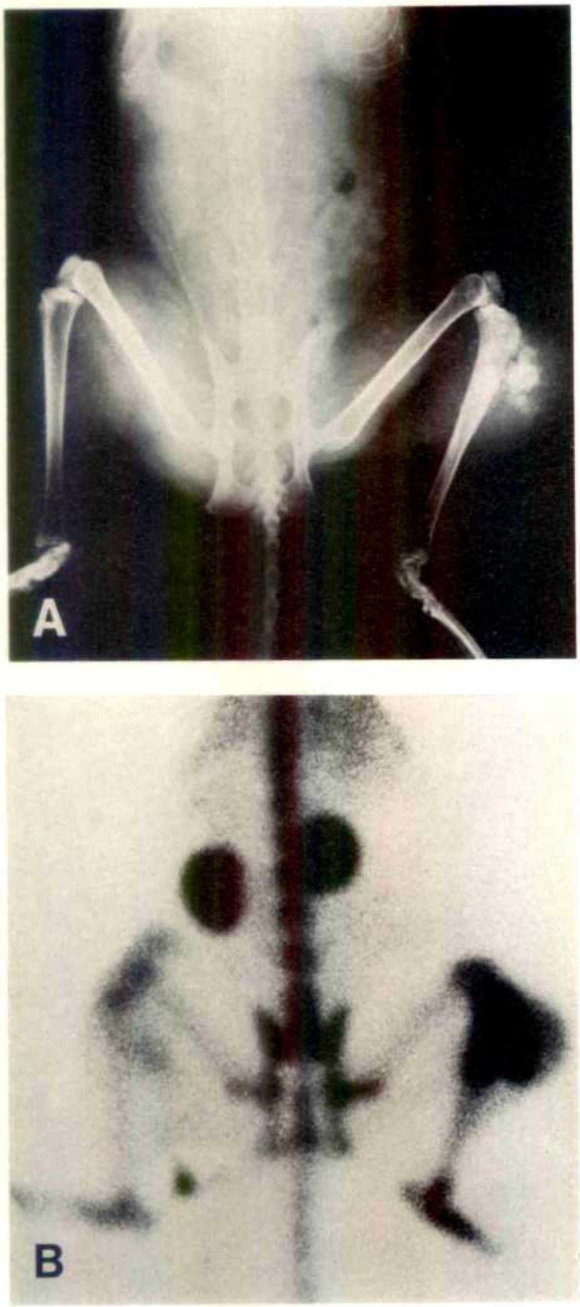

FIG. 3.

(A) Radiograph of cat with osteogenic sarcoma of left tibia.

(B) Bone scan showing increased uptake of ^{99}Tc^{m} and ^{32}P labelled condensed phosphate in tumour.

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Case reports

A major pulmonary embolus as a complication of femoral vein catheterization

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A near-fatal pulmonary embolus occurring as a direct result of femoral vein catheterization to obtain renal venous blood samples for renin estimations is reported.

CASE REPORT

A 21-year-old female with bilateral reflux nephropathy and mild hypertension was admitted for investigation in 1975. The diagnosis of bilateral gross vesico-ureteric reflux with scarring of the right kidney had been made radiologically at the age of four years. For six months prior to admission she had been taking an oral contraceptive containing norethisterone 1 mg and mestranol 0.05 mg. The blood pressure was 170/100 mm Hg supine and 150/80 mm Hg standing. The rest of the clinical examination was normal.

Renal vein sampling was carried out following frusemide stimulation with a Cordis cobra II catheter of French gauge 7.65 cm with an open end and no side holes. This was introduced into the left femoral vein using a Seldinger needle and a teflon-coated guide-wire of diameter 0.9 mm. Minimal difficulty was experienced with the initial puncture of the femoral vein. The catheter was introduced and samples obtained from both renal veins. The procedure lasted for no more than 30 minutes and concluded uneventfully.

Five days later the patient collapsed at home. On examination she was profoundly ill, being pale, cyanosed and tachypnoeic. The temperature was 36°C, the pulse was 150 beats per minute and regular, and the blood pressure was 80 mm Hg systolic. The jugular venous pressure was considerably elevated. A gallop rhythm with an accentuated pulmonary second sound was heard on auscultation. An electrocardiograph showed sinus tachycardia with an S1 Q3 T3 pattern. A radiograph of the chest was normal. Arterial blood sampled while receiving oxygen therapy at 4 l/min. via a Hudson mask showed pH 7.23 units, $PaO2$ 47 mm Hg, $PaCO2$ 43 mm Hg, $HCO3$ 18.0 m mol/l.

A pulmonary angiogram showed filling of only the superior branches of both pulmonary arteries. A major pulmonary embolus was present. Bilateral lower limb venography showed a filling defect typical of a thrombus in the left external iliac vein arising from the puncture site in the left femoral vein (Fig. 1). Streptokinase therapy was commenced within four hours and after 48 hours pulmonary angiography was repeated showing a marked improvement in the pulmonary vasculature. The patient made a full recovery and a follow-up venogram of the left leg was normal.

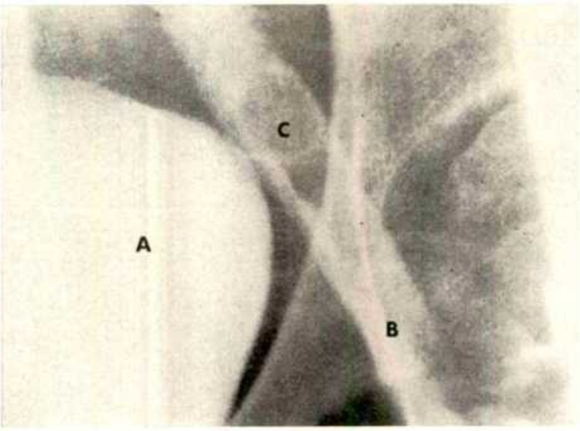

FIG. 1.

Left femoral and iliac veins (B) outlined by contrast medium. A thrombus (C) in the left iliac vein is arising from the femoral vein at the site of puncture. The bladder (A) is also outlined with contrast medium.

DISCUSSION

This is the first time that a known pulmonary embolus has occurred following numerous femoral venous catheterizations performed in this hospital. Apart from the oral contraceptive, the only other risk factor that could be identified was the femoral vein catheterization, which had been performed five days earlier. The catheter was *in situ* for less than 30 minutes and there was virtually no post-procedural immobilization. Despite the apparent paucity of risk factors, venography demonstrated a solitary thrombus near the site of catheterization. This must have been responsible for the pulmonary embolus.

In many patients receiving oral contraceptives, increased blood viscosity (Aronson *et al.*, 1971), reduced blood cell filterability (Oski *et al.*, 1972), enhanced platelet adhesiveness and aggregation (Zuck *et al.*, 1971), and increased levels of clotting factors VII and IX (Poller *et al.*, 1968) have been demonstrated.

In this instance it seems most likely that the thrombus originated at the puncture site due to the mural injury rather than on the catheter itself.

In view of the likelihood that the oral contraceptive was in part responsible for the thrombus formation in this patient, it is suggested that these drugs should be withdrawn one month prior to performing such examinations.

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An unusual regression of pulmonary metastases from embryonal carcinoma of the testis

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Spontaneous regression of testicular tumours or distant metastases from testicular cancer is extremely rare. Everson and Cole (1966) defined spontaneous regression of cancer as "the particular or complete disappearance of a malignant tumour in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on neoplastic disease".

Table I shows ten well-documented cases we found in a recent literature search for spontaneous regression of lymph nodes or distant metastases from testicular tumours. In two cases a regression of intra-abdominal or cervical lymph nodes was observed, in the others pulmonary metastases disappeared. We have treated a patient with an unusual regression of pulmonary metastases from a testicular tumour and because of the rarity of this phenomenon we wish to report and discuss this case briefly.

CASE HISTORY

A nightclub-owner, aged 38, was admitted to our Oncology Department in September 1975 because of dyspnoea, fever 39.5°C (103°F) and a cough with haemoptysis. These symptoms and enlargement of the right testis has been observed for nearly two years by the patient. He reported no pain.

On general physical examination he was a fit-looking man with normal and constant weight of 74 kg. There was neither hepatomegaly nor any supraclavicular, axillary or inguinal nodes. The left testis was normal, the right was slightly enlarged to 5×3×3 cm but not tender. Routine laboratory studies were within normal limits. Radiological examination of the chest showed large multiple pulmonary opacities in both lungs (Fig. 1). They were interpreted as metastases. An orchidectomy of the right testis was performed one week later in our Urological Department (Prof. Dr. P. Kolle). Histological examination revealed an embryonal carcinoma 3.5 cm in diameter with extensive infiltration of the funiculus cord. The histological structure of the tumour is shown in Fig. 2.

The patient returned for lymphography and chemotherapy but we were not able to convince him of the necessity of these diagnostic and therapeutic procedures. Therefore parts of the right lung including the mediastinum were irradiated using parallel opposed fields to a dose of 30 Gy (3000 rad) (uncorrected for air transmission) in 15 fractions in 29 days (cobalt-60 teletherapy unit at an SSD of 60 cm, field size 13.5×14.5 cm). A radiograph of the treatment field taken with the simulator is shown in Fig. 3.

After irradiation of the right lung there was a rather good response (Fig. 4). Pulmonary metastases in this

TABLE I

Spontaneous regressions of lymph nodes or distant metastases from testicular tumours according to a recent search of the literature

Case no.	Authors	Histological type of tumour	Spontaneous regression of
1	Birkhead and Scott (1973)	Teratocarcinoma and embryonal carcinoma	Pulmonary metastases
2	Duari (1967)	Seminoma and teratocarcinoma	Cervical lymph nodes and pulmonary metastases
3	Everson and Cole (1966)	Large round cell carcinoma	Pulmonary metastases
4	Everson and Cole (1966)	Dysembryoma	Pulmonary metastases
5	Fedon (1960)	Embryonal carcinoma	Pulmonary metastases
6	Grabstald and Rhamy (1957)	Teratocarcinoma	Pulmonary metastases
7	Jones (1966)	Embryonal carcinoma	Periaortic lymph nodes
8	Kakizoe and Ogawa (1974)	Seminoma and teratocarcinoma	Pulmonary metastases
9	Malament and Johnston (1955)	Teratocarcinoma	Pulmonary metastases
10	Smithers (1962)	Teratocarcinoma	Pulmonary metastases

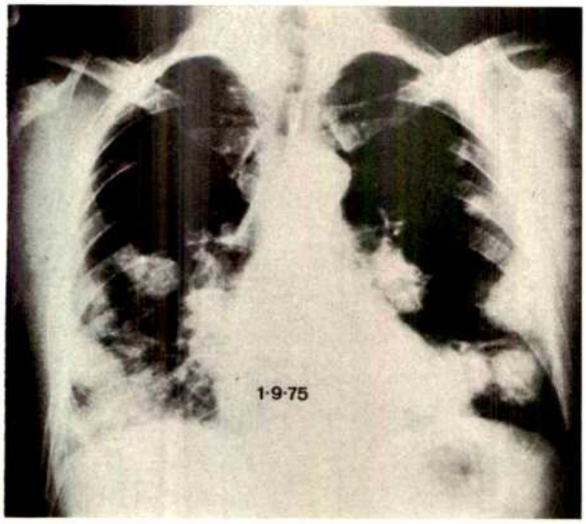

FIG. 1.
September 1, 1975. Large multiple pulmonary parenchymal nodes in both lungs before treatment.

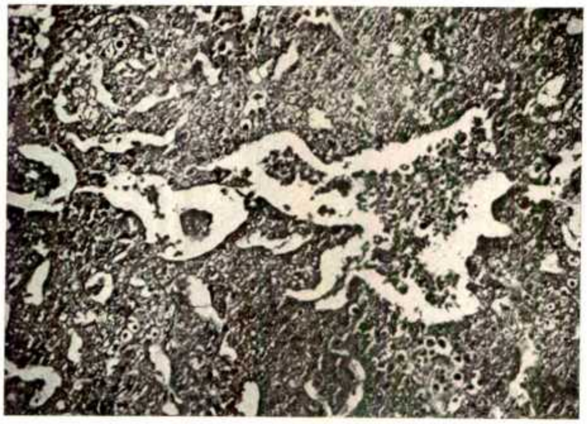

FIG. 2.
Embryonal carcinoma of the testis. Cytoplasm-rich cells are arranged mainly in solid, occasionally in tubular formations. Hematoxilin-Eosin, ×360.

area decreased but increased in the left lung. The patient did not receive any anti-tumour therapy except the radiation and he tolerated this well. He was followed up every two months. The latest chest X ray (Fig. 5), one year after surgery and radiotherapy, shows an extensive fibrosis in the right lung corresponding to the earlier irradiation fields. No conclusive evidence of pulmonary metastases could be revealed either in the right lung or in the left, the latter not having been irradiated. The patient complained of a little cough but without fever or haemoptysis and was able to work.

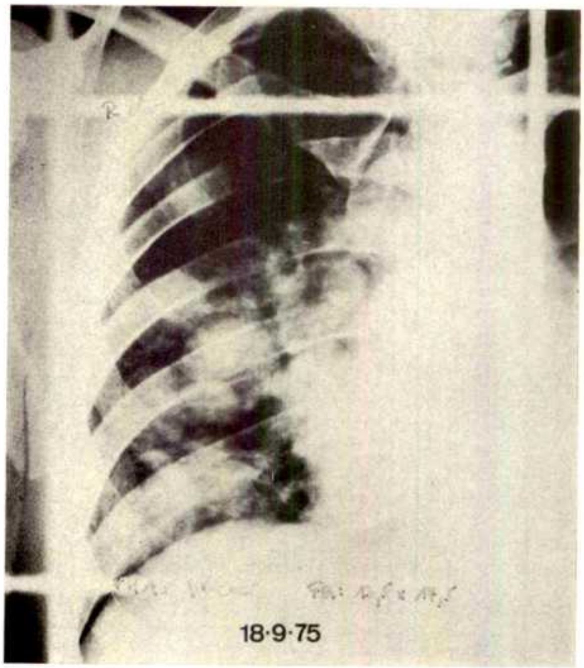

FIG. 3.
September 18, 1975. Radiograph of the treatment field taken with a simulator before radiotherapy of the right lung and mediastinum.

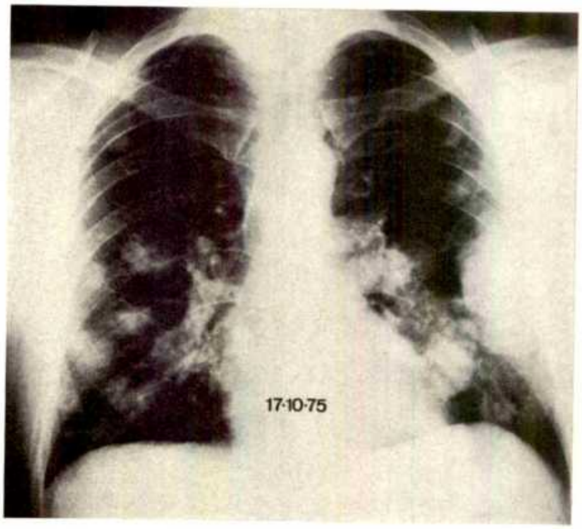

FIG. 4.
October 17, 1975. Chest X ray after radiotherapy (30 Gy, 3000 rad). Good remission of the irradiated metastases in the right lung. Number and size of nodes in the left lung have increased.

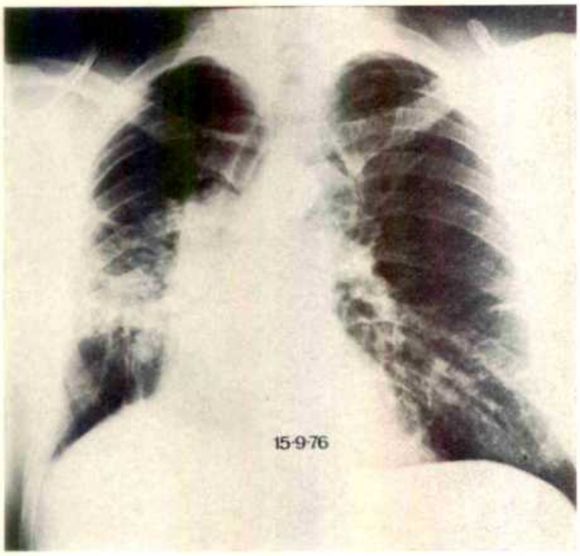

FIG. 5.

September 15, 1976. One year after therapy. Extensive fibrosis in the right lung with mediastinal displacement to the right. Linear shadowing in the left lung. No evidence of metastases in either lung.

DISCUSSION

Usually patients with pulmonary or other distant metastases from non-seminomatous testicular tumours are treated with chemotherapy, radiotherapy or both, after initial orchidectomy. Partial or complete remissions after these modalities vary from 30 to 80% (Cox *et al.*, 1972; Lo and Son, 1976; Newton and Spittle, 1969; Phillips, 1967; van der Werf-Messing, 1976). Our patient would not agree to any chemotherapy. We therefore decided to irradiate parts of the right lung and the mediastinum. The left lung was never treated in any way.

Some theories have been advanced in an attempt to explain the phenomenon of spontaneous regression of malignant tumours or metastases. In our patient we suppose that by removal of the primary tumour and by effective therapy of metastases in the right lung, the immune system had been stimulated to hyperactivity. In this way the immune system was enabled to destroy the residual metastases in the left lung.

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Aggravation of thyrotoxicosis by an iodinated contrast medium

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(*Received March, 1977*)

In recent years a few reports have appeared describing patients presenting initially with nontoxic goitre and in whom thyrotoxicosis was induced by the administration of either inorganic iodide (Connolly *et al.*, 1970; Vagenakis *et al.*, 1972) or iodinated contrast media (Blum *et al.*, 1974; Shetty *et al.*, 1974). The effect is believed to be similar to the Jod-Bbasedow phenomenom described in some patients with endemic goitre after iodide treatment (Utiger, 1972). We describe below a patient who

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presented initially with a mild hyperthyroid state which became distinctly worse shortly after cerebral arteriography.

CASE REPORT

A 74-year-old woman presented with palpitations, tremulousness and weight loss of three months duration. A few hours before she had suddenly developed weakness of the left upper and lower extremities. Physical examination revealed an afebrile conscious woman with left hemiparesis, a Babinski sign and exaggerated deep tendon reflexes on the left side. The blood pressure was 150/80 mm Hg, the pulse was irregular with a rate of 120/min. She was anxious and restless; the skin was warm and moist and there was a fine tremor of the hands. No thyroid enlargement or abnormal eye findings were noted.

An electrocardiogram showed auricular fibrillation; chest radiography revealed cardiomegaly and pulmonary congestion. Total serum thyroxin (measured by radioimmunoassay) was 25 nanomoles per dl (19.4 μg/100 ml), the normal range being 6.4–16.7 nanomoles per dl. T_3 uptake (Thyopac—3 kit method from the Radiochemical Center, Amersham) was 87% (normal range 89–117%). The condition of the patient did not permit the performance of other thyroid function tests or thyroid scanning.

The patient was managed as a case of congestive heart failure with auricular fibrillation complicated by cerebral embolism. Antithyroid treatment was not given initially because confirmation of the diagnosis of thyrotoxicosis was not available until the end of her second week in hospital. On the 16th hospital day, the left hemiparesis was noted to be worse and right carotid arteriography was performed in search for a possible cerebral haemorrhage complicating anticoagulant therapy. The arteriogram revealed only arteriosclerotic changes in the small cerebral vessels, with no evidence of a cerebral or subdural haemorrhage. Examination of the cerebrospinal fluid was normal.

Starting two days after arteriography, the patient's general condition became gradually worse, with increasing tachycardia and a rise in blood pressure. The hand tremors became more prominent and the heart failure became more severe. Serum thyroxin taken six days after the arteriogram was greater than 38.6 nanomoles per dl and T_3 uptake was 63%. Despite treatment with methimazole, propranolol, heparin and digoxin she died on the 30th hospital day.

COMMENT

The course of our patient suggests that her hyperthyroid state was markedly worse within a few days of having a carotid arteriogram when she received 20 ml. of 60% Urografin*, an amount estimated to contain 5840 mg of bound iodine. Previous reports of hyperthyroidism induced by iodinated contrast media describe this effect appearing one to three weeks after the radiographic procedure. Unlike these cases, our patient was already hyperthyroid before the procedure, and this may explain the rapidity and severity that characterized the aggravation of her thyrotoxic state.

Although high doses of iodide are in general expected to reduce acutely thyroid hormone synthesis and release (Utiger, 1972), a few patients like the above patient respond by increasing thyroid hormone levels. In some but not all of these patients a pre-existing state of iodide deficiency (a condition common in Lebanon) is believed to account for this unusual response.

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*3,5-bis-acetamido-2,4,6-triiodo-benzoic acid as sodium and megluminamido trizoate salts.

Simultaneous healing and progression of skeletal lesions in primary hyperparathyroidism

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Primary hyperparathyroidism is a condition in which more parathyroid hormone is manufactured than is needed, producing biochemical disturbances, skeletal changes and soft tissue calcification (Albright and Reifenstein, 1948). The bony lesions of hyperparathyroidism are caused by the osteoclastic resorption of bone, associated with fibrosis and poorly calcified new bone. Localized accumulation of fibrous tissue and giant cells may occur called "brown tumours". Occasionally these tumours may

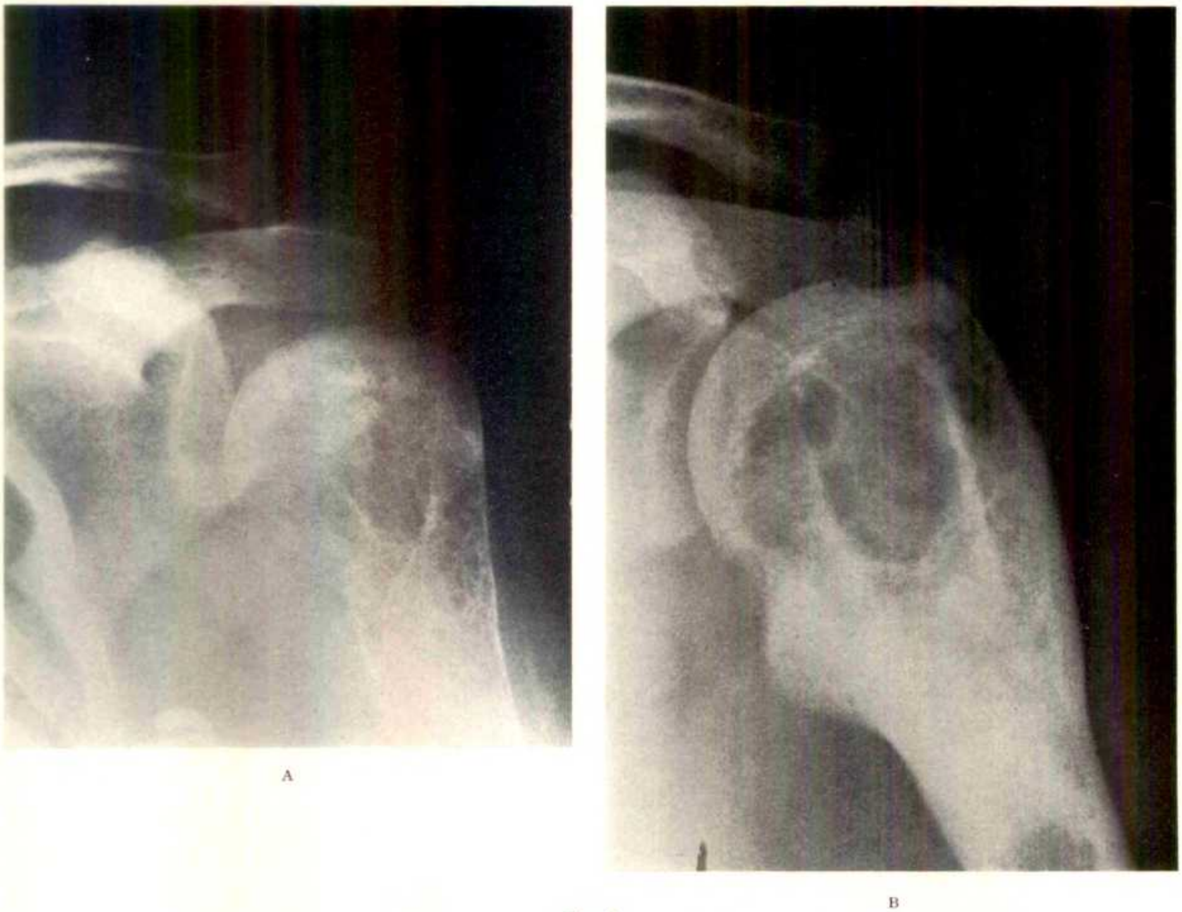

FIG. 1

(A) Brown tumour with fracture in the left humerus in 1971.
(B) Same lesion in 1973 showing healing by sclerosis.

undergo necrosis and liquefaction (Steinbach *et al.*, 1961). The reported incidence of brown tumours is variable and probably falling due to improvement in the diagnostic techniques for hyperparathyroidism (Genant *et al.*, 1973).

In order to permit healing of the bones in primary hyperparathyroidism surgical treatment of the glandular abnormality is required (Reiss, 1970). A case of untreated primary hyperparathyroidism is reported in which there was healing of a brown tumour following fracture, whereas the other bony lesions of the disease showed rapid progression.

CASE REPORT

A 53-year-old female complaining of a painful left shoulder of two months duration presented in June, 1971. No other abnormality was detected on physical examination. Radiology demonstrated a well defined loculated osteolytic lesion in the upper end of the left humerus (Fig. 1A). There was a fracture present at the level of the surgical neck. Biopsy showed the histological features of a brown tumour of hyperparathyroidism. The serum calcium (3.52 mmol/l) and the alkaline phosphatase (116 i.u.) were elevated. The blood urea (5.8 mmol/l) was normal. A skeletal survey showed two well defined radiolucencies in the left femur and sub-periosteal erosions of the phalanges (Fig. 2A). The findings suggested primary hyperparathyroidism, but further investigations and treatment were refused.

In October, 1973 the serum calcium was still elevated (3.31 mmol/l) and the alkaline phosphatase had risen to 375 i.u. Sub-periosteal erosions were more marked and brown tumours were seen in the pelvis (Fig. 2B). The lesion in the left humerus was reduced in size with sclerosis and healing of the fracture (Fig. 1B). A ten-day course of hydrocortisone failed to suppress the serum calcium.

A skeletal survey in September, 1974 showed brown tumours in the pelvis (Fig. 3), right humerus and ribs but no change in the left humeral lesion. The patient agreed to treatment. She received 10000 units of Vitamin D_3 daily for ten days, and at surgical exploration a large, left inferior parathyroid adenoma was removed. The right superior gland was not identified but the other glands appeared normal.

Post-operatively the serum calcium and the alkaline phosphatase returned to normal and there was a generalized increase in bone density over a period of a year. Some of the brown tumours remained unchanged whereas others were

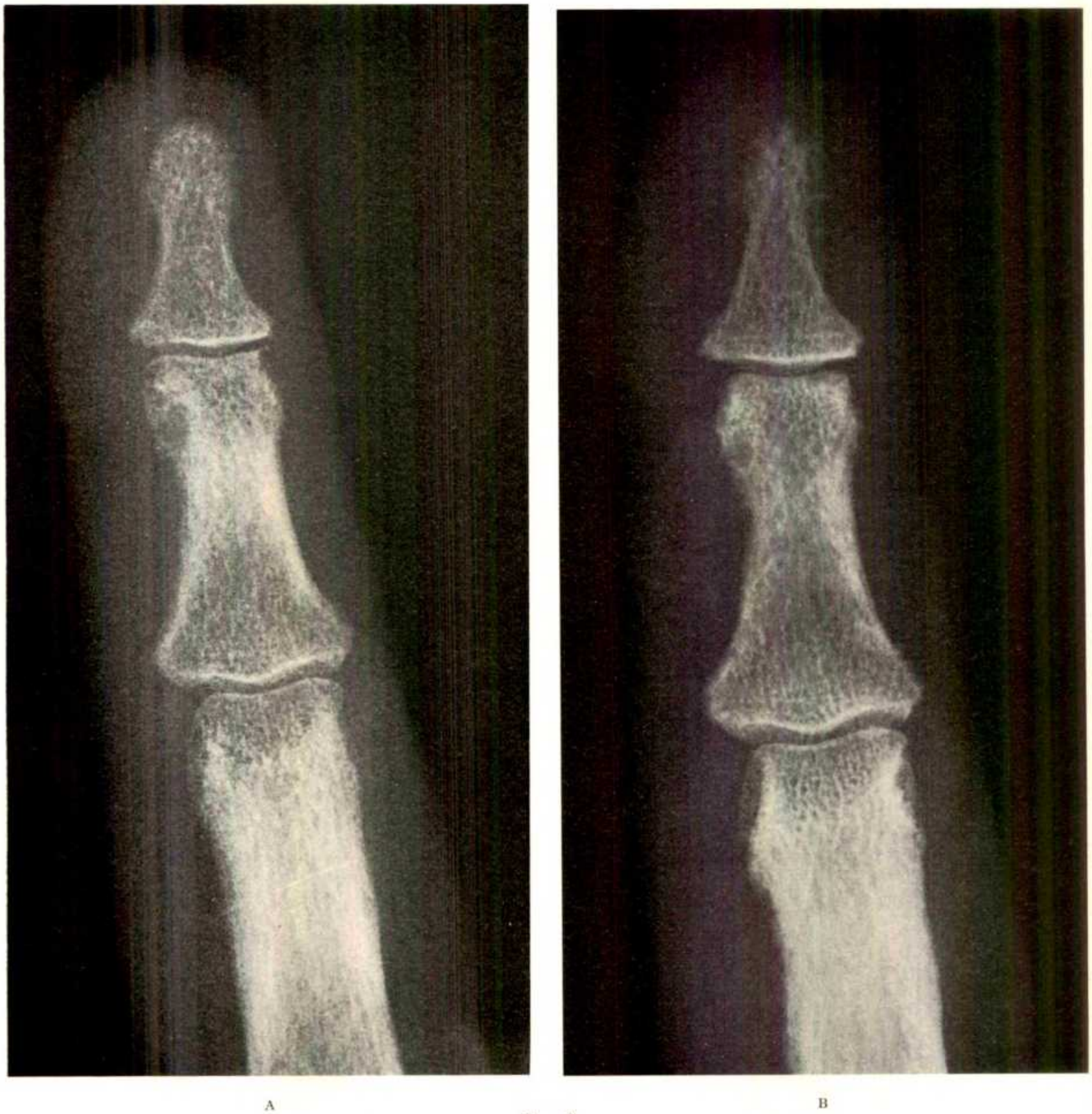

FIG. 2

(A) Right index finger with minor sub-periosteal erosions in 1971.

(B) Same finger in 1973 showing progression of the sub periosteal erosions including marked erosion of the terminal tuft.

replaced by normal and sclerotic bone. The left humeral lesion showed no further change. Follow up until 1976 revealed no recurrence of the disease.

DISCUSSION

The bony lesions of hyperparathyroidism heal rapidly following parathyroidectomy, radiological improvement being often noted within four to six weeks of treatment. Recalcification begins at the periphery with replacement of the brown tumour by dense bone, the originally decalcified areas becoming denser than normal bone, producing exaggerated striations (Steinbach *et al.*, 1961).

Healing of bony lesions may occur following vitamin D therapy (Woodhouse *et al.*, 1971) prior to parathyroidectomy and local healing of the brown tumours of primary hyperparathyroidism has occurred following complete curettage or radiotherapy (Steinbach *et al.*, 1961).

1977, *British Journal of Radiology*, *50*, 674–676

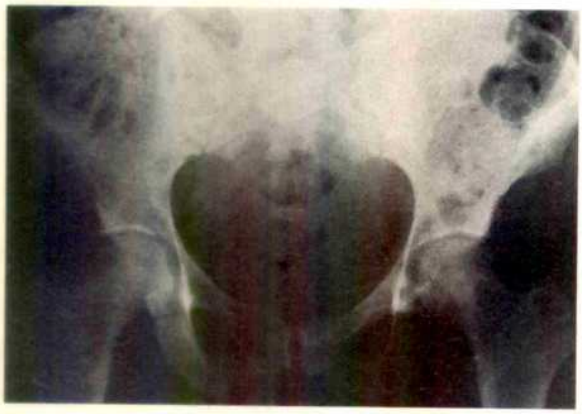

FIG. 3.
Multiple brown tumours in the pelvic bones in 1974 prior to surgery.

An isolated case of spontaneous healing of the bone lesions of primary hyperparathyroidism has been reported by Linden (1934). A man with marked bone changes had a spontaneous recovery over a period of a year. Blood calcium was not estimated initially, but was abnormally high during the period of resolution of the bone lesions. No other reference to the spontaneous healing of bone lesions in untreated primary hyperparathyroidism has been found in the literature.

In our case of untreated hyperparathyroidism a brown tumour healed with irregular sclerosis. During the time of healing there was progression of the other skeletal manifestations of the disease and persistent biochemical abnormalities. This suggests that with the periosteal involvement and callus formation initiated by the recent trauma, the osteoblastic activity was locally dominant to the underlying osteoclastic process of primary hyperparathyroidism. Similar bone changes with healing after fracture have been reported in experimental hyperparathyroidism in young guinea-pigs (Jaffe *et al.*, 1932).

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Mammographic evidence of breast cancer control with humoral and chemotherapeutic treatment

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The mammographic manifestations of carcinoma of the breast are well known (Witten, 1969; Wolfe, 1972). To the best of our knowledge mammographic evidence of alterations of the appearance of a breast cancer in a patient receiving hormonal manipulation and chemotherapy have not been described. A case illustrating nearly complete regression of the xeromammographic evidence of a breast cancer is presented.

CASE HISTORY

A 55-year-old female presented in February 1975 with severe thoraco-lumbar spine pain of one year duration. Biopsy material obtained at another hospital disclosed intraductal carcinoma of the right breast. A xeromammogram obtained at this time showed typical findings of breast cancer

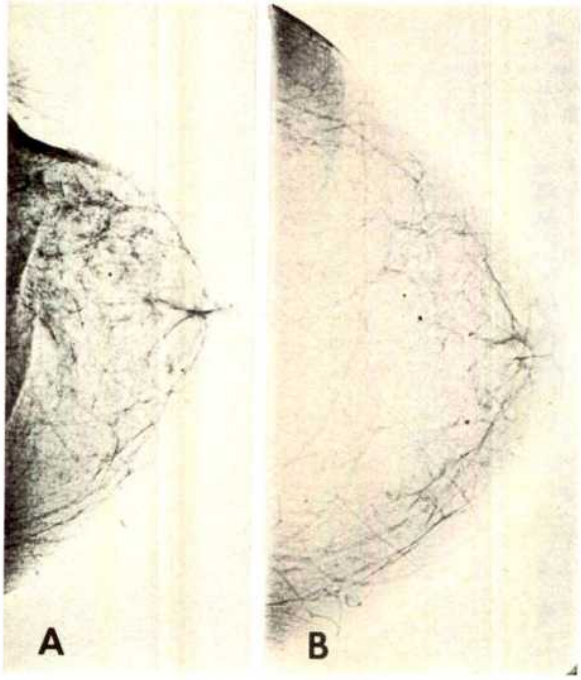

FIG. 1.
Xeromammogram of the right breast before treatment (A) and after treatment (B).

including increased density, malignant calcifications, distortion of the breast's architecture, skin thickening and retraction as well as some post biopsy distortion (Fig. 1A). The axial skeleton showed roentgenographic evidence of extensive bone metastases.

Bilateral adrenalectomy and oophorectomy were performed in March 1965. At surgery, metastases were discovered in both ovaries, the spleen, the right adrenal gland and the liver. Chemotherapy was begun with fluorouracil, adriamycin, and cyclophosphamide (FAC) (Blumenschein *et al.*, 1974). Five courses of FAC were administered between April and December 1975. Xeromammogram in July 1975 showed partial resolution of the malignant changes. The vertebral metastases were unchanged.

In December 1975 maintenance chemotherapy utilizing cyclophosphamide, methotrexate, and fluorouracil (CMF) was begun. Repeat xeromammogram in November 1976 showed almost complete resolution of the malignant changes. Minimal skin thickening remained near the inframammary fold (Fig. 1B). Radiographs of the spine showed regression of the metastases and reversion to a nearly normal osseous appearance.

DISCUSSION

This case presented an opportunity to observe the effects of humoral manipulation and chemotherapy on a breast cancer without the superimposed effects of radiation therapy.

The disappearance of the cancer and desmoplastic reaction were manifested xeromammographically by decreased density, return to a normal

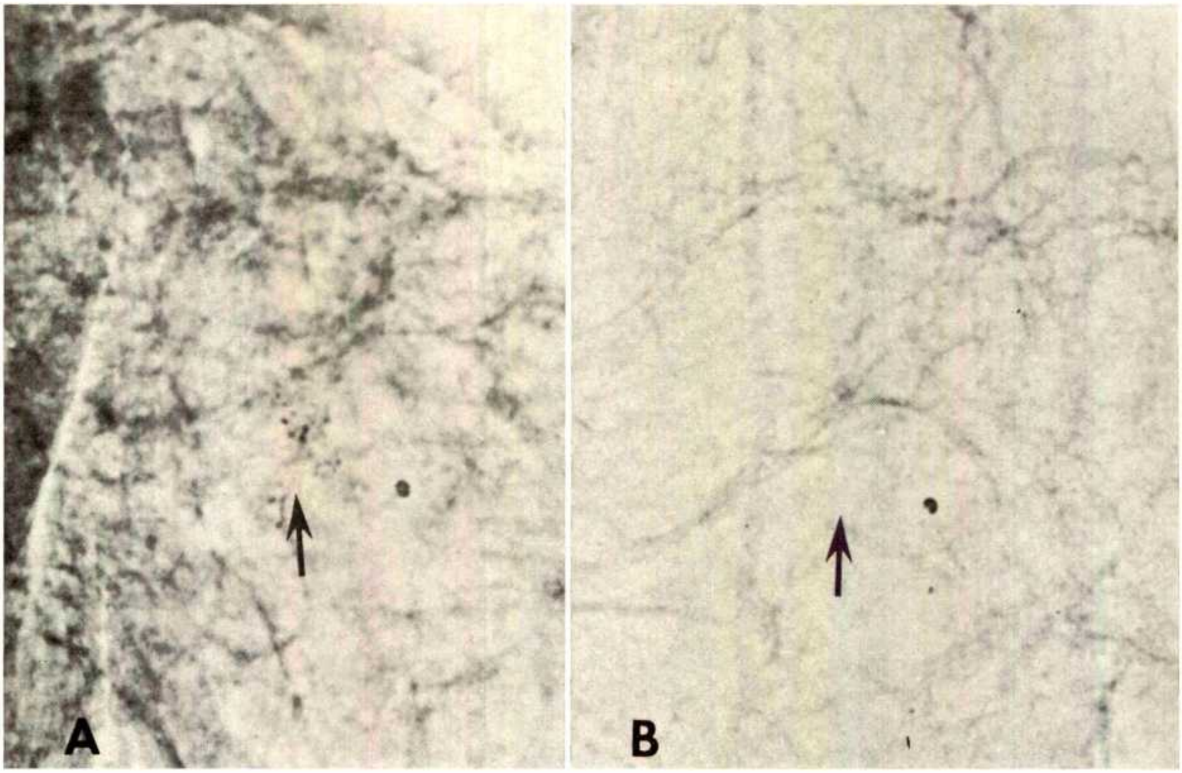

FIG. 2.
Magnification of xeromammogram before treatment (A) and after treatment (B). The malignant calcifications (→) have disappeared on the later films.

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breast architecture, and disappearance of skin retraction. Particularly interesting was the nearly complete disappearance of the malignant calcifications (Fig. 2). This has been noted previously following radiation therapy (Libshitz *et al.*, 1976). The persistence of slight skin thickening may reflect some residual lymphatic involvement by the malignancy.

Mammography provided an excellent means of assessing tumour response to humoral manipulation and chemotherapy in this patient. It is suggested that mammography be further utilized in assessing tumour response in patients with a breast cancer still present in whom medical management is undertaken.

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Cervico-mediastinal thymic cyst: cyst puncture and contrast radiographic demonstration

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Positive contrast demonstration of a cervical or cervico-mediastinal thymic cyst has not been previously reported. The following is an account of the findings of a cyst puncture and water soluble positive contrast demonstration of the more rare cervico-mediastinal thymic cyst.

Case Report

A six-year-old boy presented to surgical out-patients because of an asymptomatic swelling on the right side of his neck. This swelling only became apparent when he strained or performed the Valsalva manoeuvre. There was a history of the boy being lassooed about the neck and being pulled from his bicycle nine months before. His mother noticed the swelling two weeks after this episode when he coughed or became excited. There was no change in his general good health. The swelling had not changed in size, but the patient had become more adept at demonstrating it. The lump was apparent only when intra-thoracic pressure was raised. It then appeared from behind the right clavicular notch of the manubrium sterni and extended almost up to the angle of the right mandible, lying antero-medial to the sterno mastoid muscle (Fig. 1). It felt soft and cystic and disappeared immediately on stopping the Valsalva manoeuvre. There was no bruit on auscultation.

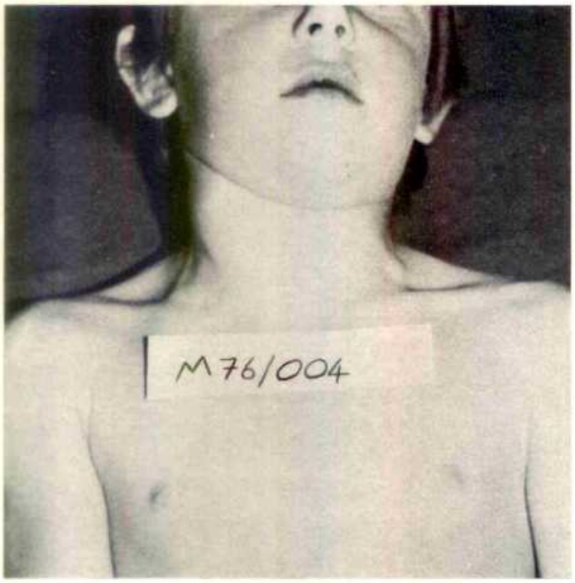


Fig. 1.

Swelling of right side of neck as seen during sustained Valsalva manoeuvre.

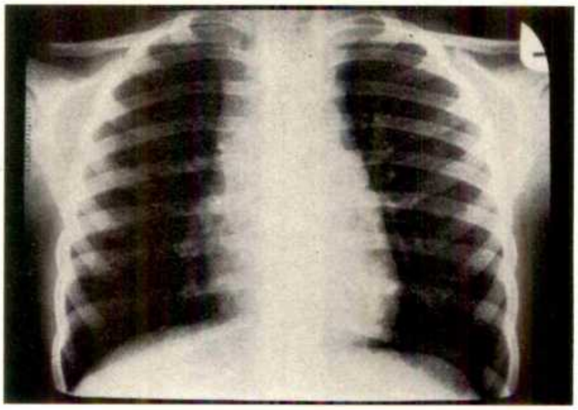


Fig. 2.

Chest radiograph showing widening of superior mediastinum.

P.A. chest radiograph showed some widening of the upper mediastinum (Fig. 2). There was slight deviation of the trachea to the left. Barium swallow was normal. There was no evidence of gas in the swelling during screening or on spot films.

As the patient was co-operative and could sustain his Valsalva manoeuvre for more than 30 seconds it was decided the swelling could be needled. The skin was infiltrated with 2 ml 2% Lignocaine, using a 25 gauge needle, over the site of maximal swelling. A 21 gauge "Butterfly" needle was then used to puncture the cyst. 5 ml clear straw-coloured fluid was aspirated. 10 ml Conray 280 was then injected into the cyst and the needle removed. A.P. and lateral radiographs were then taken, centred on the thoracic inlet using an over couch tube, during the Valsalva manoeuvre and at rest (Fig. 3A, B, C). The cyst measured 10.5 cm in length and extended from the hyoid bone into the anterior portion of the superior mediastinum through a wide channel 2 cm in diameter. The size of the intra- and extra-thoracic portions of the cyst varied during the Valsalva manoeuvre. The cyst wall was smooth and the cardiac surface slightly loculated.

Eight hours after the procedure the neck became tender over the swelling and the patient developed a pyrexia of 38°C. WBC at this time was 15 100, 62% polymorphs, 33% lymphocytes. He was given Ampicillin Syrup 125 mg, four times daily for five days. The pyrexia settled within 24 hours and the neck tenderness within four days. Six weeks later the patient was re-admitted for operation, his neck swelling unchanged from when first seen.

At operation an elongated cystic and solid benign lesion measuring about 12 × 3 cm was excised. This extended from the angle of the jaw to the second costal cartilage. The upper portion appeared to be connected to the salivary gland, the lower end to the thymus. It was well encapsulated. The patient made an uneventful recovery, being discharged after ten days.

The pathological report on the specimen was that of a congested elongated cystic lesion. It had a yellow fatty area within its wall. The cyst contained brownish yellow fluid. Microscopically the cyst wall showed the structure of hyaline fibrous tissue. Small blood vessels were present. There was a major loculus and subsidiary loculi. The cyst wall was lined by a single layer of flattened epithelium. Lymphatic foci were present, together with haemosiderin deposits, cholesterol clefts and foreign body giant cells. In the more solid areas normal thymic tissue was seen. Hassell's corpuscles were prominent and reticulum cells were seen. There was no evidence of malignancy. The appearance was that of a thymic cyst.

DISCUSSION

The neck is a common site for the occurrence of cystic masses. Most develop from anomalies of the pharyngeal pouches and branchial clefts. They can be classified as branchial, thyroglossal, thyroid, parathyroid, thymic, dermoid and hygromic cysts (Albers, 1963). Thymic cysts derived from a remnant of the third and sometimes fourth branchial pouch,

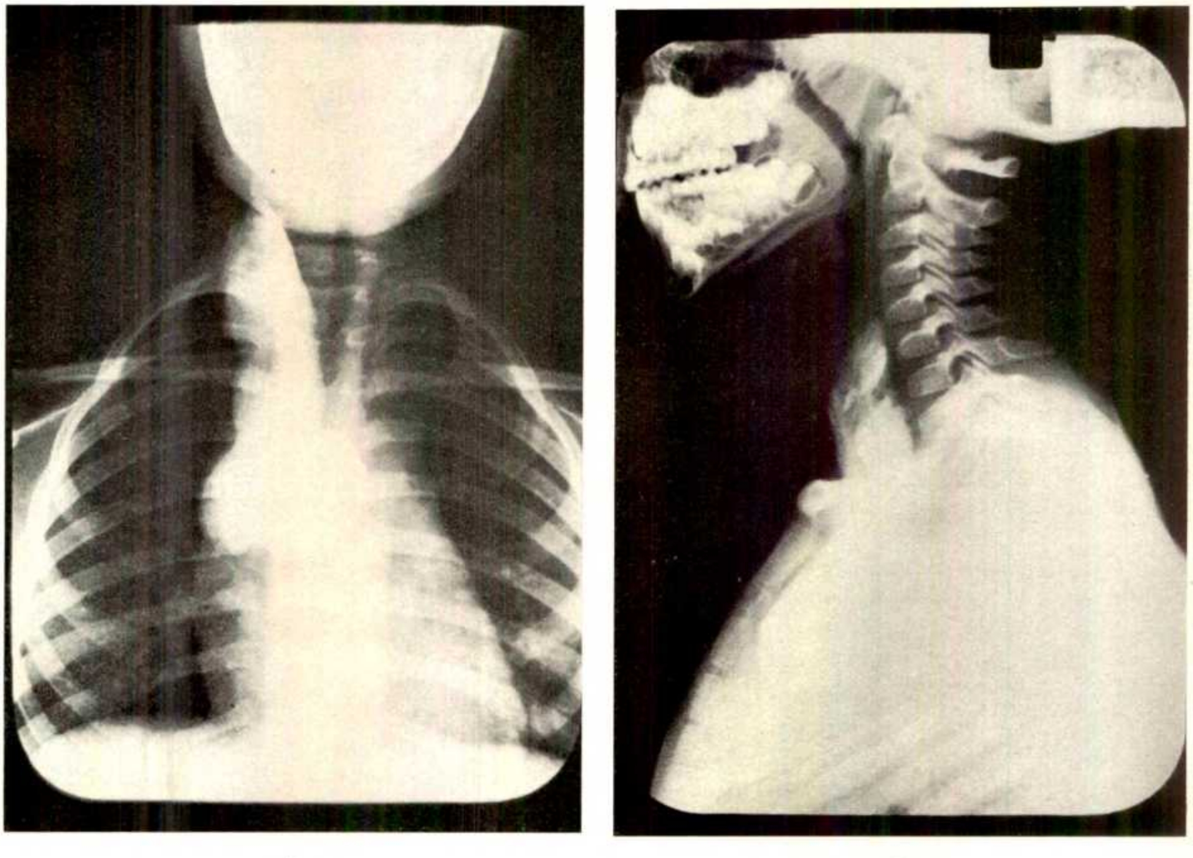
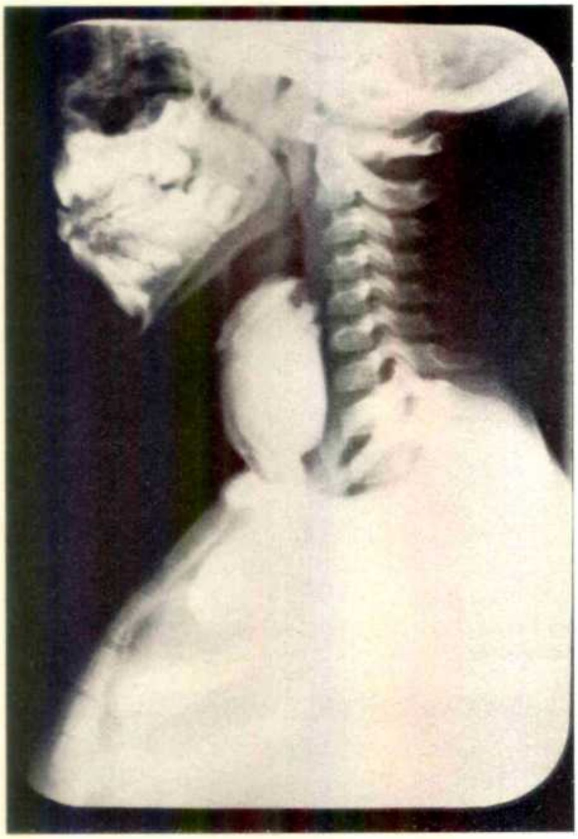

A B

FIG. 3.



C

Fig. 3.

Radiographs of chest and neck demonstrating the contrast filled thymic cyst. (A) and (B) represent A.P. and lateral views at rest. (C) demonstrates the extent of filling of the neck portion during the Valsalva manoeuvre.

can occur in the neck or mediastinum (Ackerman and Rosai, 1974). It is pointed out that a large proportion of "non-specific cysts" of the antero-superior portion of the mediastinum are probably of thymic origin. The only distinguishing feature of thymic cyst is the presence of thymic tissue in the wall. The epithelial lining may be squamous or columnar. Degenerative changes are common, with prominent cholesterol granulomas. A comprehensive review of thymic cysts and cystic thymomas was carried out by Dyer (1967). He stressed that care should be exercised in excluding the possibility of thymoma with cystic degeneration. In his review he concluded that the neck was an uncommon site for thymic cysts. Cervical thymic cysts can be seen anywhere along a line extending from the angle of the mandible to the manubrium sterni (Ratnesar, 1971). Podolsky *et al.* (1962), in their review of 39 thymic cysts, gave their incidence as mediastinal 27, cervical 8, and combined 4. Mikal (1974), in presenting the 34th case of cervical thymic cyst, gives a good account of the embryogenesis. The age incidence shows that the majority present within the first decade of life. Few cases of combined cervical and mediastinal thymic cysts have been reported since that by Pezcoller (1929). This is the first reported radiographic contrast demonstration. Behring and Bergman (1963), drew attention to the value of plain radiographic examination of a cervical cyst, particularly to show any mediastinal extension. Preoperative cyst puncture and contrast examination will give additional information as regards the site, location and extent of the cyst and will be valuable to the surgeon prior to surgical intervention. It seems reasonable to obtain this further information by direct cyst puncture when dealing with a cystic mass.

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Short communications

The oxygen enhancement ratio for high energy neutrons*

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Neutron beams currently used for radiotherapy range from 16 MeV deuterons on beryllium at Hammersmith to 67 MeV protons on beryllium at the Fermilab; over this range the oxygen enhancement ratio (OER) appears to be constant at about 1.6 (Hall, 1975a, b; Hall *et al.*, 1974b, 1975, 1977). Recent reports of studies with cyclotron-produced neutrons of higher energy at the University of Maryland indicate lower OER's of 1.3 and 1.2 for 80 MeV deuterons and 101 MeV protons on beryllium respectively (Harrison *et al.*, 1975, 1976). The possibility that higher energies may result in lower OER values is obviously of great interest and importance from the point of view of choosing the energy range for additional clinical facilities.

We have recently had the opportunity to make radiobiological measurements on the neutron beam produced by 80 MeV deuterons on Be at Maryland. Unfortunately the 101 MeV proton beam will not be available in the near future due to technical difficulties with the cyclotron. However, it was considered worthwhile to report the data for the 80 MeV beam without delay because of the practical importance of the result, and in view of the fact that the data of Harrison *et al.* (1975, 1976) have been widely quoted.

The two biological test systems chosen are well tried and have been used to measure OER values over a wide range of neutron energies, including several of the beams currently used for radiotherapy.

First, the growth inhibition of *Vicia* seedlings. The seedlings were held in a specially constructed holder, fabricated of lucite but with an entrance window of tissue equivalent plastic 2.5 cm thick, in which build-up of secondary particles could occur. The holder was gassed vigorously with air or

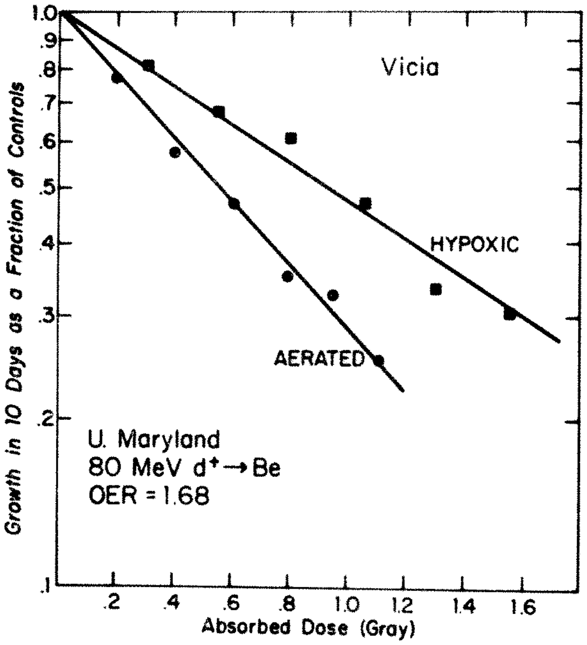

FIG. 1.

Dose response curves for growth inhibition of the primary root of *Vicia* seedlings irradiated under aerated and hypoxic conditions with neutrons generated by 80 MeV deuterons on a beryllium target.

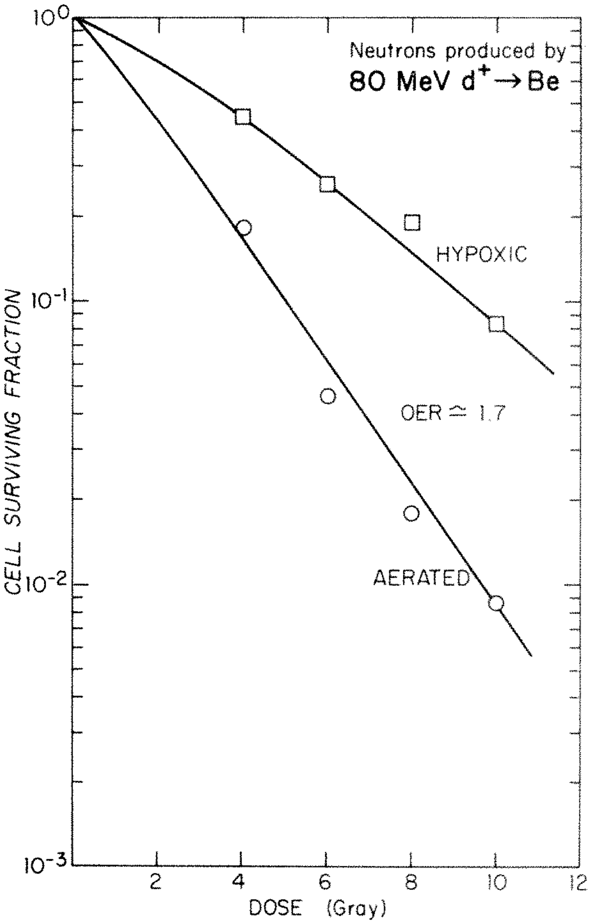

FIG. 2.

Survival curves for V79 Chinese hamster cells irradiated under aerated and hypoxic conditions with neutrons generated by 80 MeV deuterons on a beryllium target.

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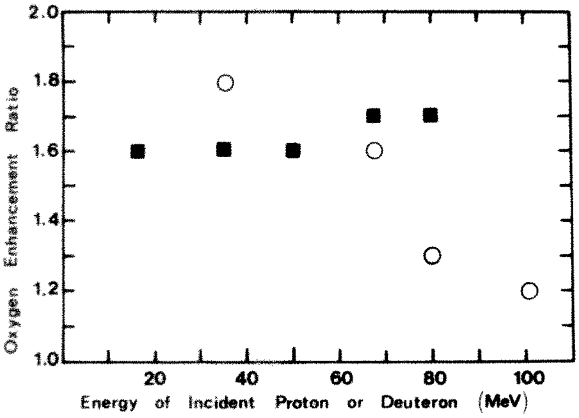

FIG. 3.

Oxygen enhancement ratios for various neutron beams produced by bombarding a beryllium target with protons or deuterons. Open circles represent data from Harrison *et al.*, 1976. Closed squares represent data reported here, or from Hall, 1975 and Hall *et al.*, 1974b and 1977.

high purity nitrogen during irradiation and for 20 minutes beforehand to render the seedlings well oxygenated or hypoxic. The technique has previously been described in detail (Hall and Cavanagh, 1967; Hall *et al.*, 1974b). Dose response curves for inhibition of root growth under aerated and hypoxic conditions are shown in Fig. 1. The OER is approximately 1.7.

The second biological system used was a line of V79 Chinese hamster cells cultured *in vitro*. Cells were irradiated while sealed in glass ampoules which were vigorously shaken during irradiation to keep the cells in suspension and prevent them from settling out on the glass surface. Hypoxia was achieved by using a high cell concentration (2×10^6 cells in 1 ml of medium), flushing the air from the ampoule with a mixture of 5% CO_2 in nitrogen, and then incubating the sealed ampoule for one hour at 37.5°C so that residual oxygen was scavenged from the system by cell respiration. A second series of ampoules contained 10^4 cells and remained aerated. This technique has also been described in detail (Hall *et al.*, 1974a, 1975). After irradiation, the ampoules were opened and aliquots of the cell suspension replated to test for colony formation. Survival curves under aerated and hypoxic conditions are shown in Fig. 2. The OER is approximately 1.7.

The OER values reported are plotted in Fig. 3, together with other data obtained with the same test systems on other cyclotrons used for radiotherapy. Results from the various machines are summarized in Table I. For comparison, the data of Harrison *et al.* (1976) are also shown in Fig. 3. Our experiments show no indication of a decreasing OER with increasing neutron energy.

TABLE I

OER MEASUREMENTS WITH NEUTRON BEAMS PRODUCED BY DEUTERONS OR PROTONS ON BERYLLIUM

Accelerator	Accelerated particle	Particle energy (MeV)	OER	
			Vicia	V79 hamster cells
Naval Research Lab.	deuteron	16*	1.6	—
		35	1.6	1.5
TAMVEC	deuteron	50	1.6	—
Fermilab	proton	67	1.7	1.7
Univ. Maryland	deuteron	80	1.7	1.7

* This energy was obtained at NRL, but intended to simulate the Hammersmith Cyclotron.

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With pleasure we record the help and cooperation of Dr. George Harrison, Dr. Harry Holgren and the staff of the Maryland Cyclotron in performing these experiments.

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Short communications

Optimal radiotherapy of tumour cells following exponential-quadratic survival curves and exponential repopulation kinetics

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A previous paper (Wheldon and Kirk, 1976) presented the mathematical derivation of optimal treatment schedules in radiotherapy, assuming a single-hit multi-target radiation survival curve (see Elkind and Whitmore, 1967) and exponential repopulation kinetics for tumour cells, and utilizing the Cumulative Radiation Effect (CRE) representation of radiation damage to normal connective tissue (Kirk *et al.*, 1971).

Recently, attention has been focused on cell survival curves which, contrary to the multi-target model, have non-zero initial slopes (Alper, 1975). Some evidence favours an exponential-quadratic survival curve with non-zero initial slope and continuously steepening slope as radiation dose increases (Neary, 1965; Sinclair, 1969; Kellerer and Rossi, 1971; Chadwick and Leenhouts, 1973; Douglas and Fowler, 1975). This form, the exponential-quadratic form, though not dependent essentially on any theory, can be derived from a molecular theory of radiation damage which emphasizes the role of radiation-induced single-strand and double-strand breaks in chromosomal DNA (Chadwick and Leenhouts, 1973).

The present paper presents an analytical derivation of optimal treatment schedules for the radiotherapy of tumour cells following the exponential-quadratic form of survival curve, other assumptions being as before (Wheldon and Kirk, 1976).

With exponential-quadratic survival and exponential repopulation by surviving cells, the fraction of cells (σ) surviving N treatments, each of d rad, administered with inter-treatment times of t days, is:

$$\sigma = \mathrm{Exp}\ \{N\ (\lambda t - \alpha d - \beta d^2)\} \quad \dots\dots(1)$$

where α and β are the survival curve parameters and λ is the exponential repopulation constant for surviving cells. If the number of treatments is limited by the radiation tolerance of normal connective tissue, and this is assessed on the CRE system (Kirk *et al.*, 1971), the maximum number of treatments is

$$N_{\max} = \left(\frac{d}{R_f^{\max}}\right)^{-1/a} t^{b/a} \quad \dots\dots(2)$$

where $a = 0.65$, $b = 0.11$ and $R_f^{\max}$ is the numerical value of the CRE for connective tissue tolerance.

Substituting $N_{\max}$ in (2) for N in (1) we obtain σ_f, the *final* surviving fraction when the treatment schedule is terminated. This is:

$$\sigma_f = \mathrm{Exp}\left\{\left(R_f^{\max}\right)^{1/a}\left(\lambda . d^{-1/a} . t^{1+b/a} - \alpha d^{1-1/a} . t^{b/a} - \beta . d^{2-1/a} . t^{b/a}\right)\right. \quad ..(3)$$

To obtain the *optimal* dose per treatment (d^*) and the *optimal* interval between successive treatments (t^*) we must simultaneously solve the equations

$$\left.\frac{\partial\ (\sigma_f)}{\partial d}\right|_{d=d^*} = 0 \quad \dots\dots(4)$$

$$\left.\frac{\partial\ (\sigma_f)}{\partial t}\right|_{t=t^*} = 0 \quad \dots\dots(5)$$

choosing only physically meaningful solutions yielding a minimum for σ_f.

We obtain:

$$d^* = \frac{\alpha\{1-(a+b)\}}{\beta\{2(a+b)-1\}} \quad \dots\dots(6)$$

and

$$t^* = \frac{b\{\alpha d^* + \beta(d^*)^2\}}{\lambda\ (a+b)} \quad \dots\dots(7)$$

Substituting $a = 0.65$ and $b = 0.11$ and setting $\tau = \frac{0.69}{\lambda}$ where τ is tumour doubling time (in days) we find

$$d^* = 0.46\ \frac{\alpha}{\beta}\ \text{rad} \quad \dots\dots(8)$$

$$t^* = 0.14\ \frac{\alpha^2}{\beta}\ \tau\ \text{days} \quad \dots\dots(9)$$

from which optimum treatment schedules can easily be calculated.

For illustrative purposes we have calculated optimal schedules for hypothetical tumour cell populations with survival curve parameters $\alpha = 2.0 \times 10^{-3}$ rad^{-1} and $\beta = 4.0 \times 10^{-6}$ rad^{-2}, and a range of doubling times. The parameter values chosen are close to those reported for a

TABLE I

COMPARISON OF OPTIMAL AND CONVENTIONAL SCHEDULES

Doubling time (τ days)	Optimal dose (d^* rad)	Optimal interval (t^* days)	Treatment number ($N_{\max}$)	Optimal surviving fraction	Conventional surviving fraction
1	230.8	0.14	17.28	5×10^{-5}	5.4×10^{1}
10	230.8	1.41	25.51	4×10^{-7}	4×10^{-7}
30	230.8	4.23	30.72	3×10^{-8}	1×10^{-7}
70	230.8	9.86	35.46	1×10^{-9}	7×10^{-8}
100	230.8	14.09	37.66	4×10^{-10}	6×10^{-8}
150	230.8	21.13	40.34	8×10^{-11}	6×10^{-8}

Survival parameters: $\alpha = 2.0 \times 10^{-3}$ rad^{-1}, $\beta = 4.0 \times 10^{-6}$ rad^{-2}.
Conventional schedule: $d = 200$ rad, $t = 1$ day, $N_{\max} = 30$.

"typical" line of mammalian cells (Chinese hamster ovary cells) growing in culture (Chadwick *et al.*, 1976).

Table I gives the optimal schedule parameters and schedule effect on tumour cells for this case. The CRE value (R_f^{max}) is 1825 radiation effect units (REU), a value close to tolerance of normal connective tissue, and attained on completion of a more conventional schedule consisting of 30 treatments, administered daily, each of 200 rad. The effects of the conventional schedule on the tumour cell populations of different doubling times are also given for comparison.

While no great stress should be placed on the numerical details, it is of interest that (for this cell line) optimal scheduling appears to be advantageous for very fast and very slowly growing tumours, but differs little from conventional therapy for doubling times in the region of ten days. It should be appreciated, of course, that many tumours may follow Gompertzian rather than exponential growth kinetics, the growth rate accelerating as the tumour size is reduced by treatment.

This suggests a non-uniform treatment schedule, the inter-fraction time reducing progressively as treatment proceeds. Analysis of this case is currently in progress.

The present analysis permits deduction of theoretically optimal schedules where an exponential-quadratic function constitutes a better fit to the available data than the more conventional multi-target function. Where the two functions provide equally good fits to the available data it is to be expected that the same optimal schedules would be predicted in each case, provided the theoretical optimum falls within a region of the survival curve for which experimental data are available.

The possibility arises, of course, that one or other of the alternative representations leads to the prediction of an optimum dose which lies outside the experimentally documented region of the survival curve (*i.e.* involves extrapolation of the mathematical representation into experimentally uncharted areas), in which case experimental investigation of the region concerned would be necessary in order to verify that the representation remained valid.

It is of interest to note that the optimal dose obtained (231 rad) for the "typical" cell line considered here is in a well-documented region of the survival curve and could have been equally-well deduced from a multi-target representation with parameter values $n=1.6$ and $D_0=225$ rad. The equivalence of optimum schedules derived from the two representations need not hold for cells with more unusual parameter values, in which case a decision as to which representation is appropriate becomes necessary.

As with the multi-target analysis (Wheldon and Kirk, 1976), the analysis fails for the case of a purely exponential "shoulder-less" survival curve, the optimum dose predicted by equation (6) increasing without limit as the quadratic parameter tends towards zero. The exponential curve is indeed a special case which requires separate consideration and will be treated in a forthcoming publication.

We must emphasize, as before, that the parameter values quoted pertain to *hypothetical* tumour cells *in vivo* and that the numerical calculations presented are intended as illustrations of the method and not as recommendations for departures from conventional practice in clinical radiotherapy. More realistic models, incorporating non-exponential tumour growth, non-uniform scheduling, and the optimal therapy of mixtures of oxic and hypoxic tumour cells, will be presented in future papers.

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1977, *British Journal of Radiology*, *50*, 683–685 SEPTEMBER 1977

Proceedings of The British Institute of Radiology

Recovery and repair

Abstracts of papers read at the Radiobiology Work-in-Progress meeting held on Friday, May 20, 1977 at the Reid-Knox Hall, Institute House, 32 Welbeck Street, London W1M 7PG

Elkind recovery and "sub-lethal damage": a misleading association? by Tikvah Alper.
Recovery from sub-lethal and potentially lethal damage in tumours, by N. J. McNally.
Evidence for location of the site of accumulation of sub-lethal damage, by P. Bryant and Jane Parker.
The qualitative recovery in haemopoietic stem cells, by P. Schofield.
Studies on a DNA containing material from P388 cell lysates, by D. G. Poppitt and B. W. Fox.
Extensive and equivalent repair in both resistant and sensitive *E. coli* determined by a DNA unwinding technique, by W. A. Cramp, A. M. George, and G. Ahnstrom
The time course of post-irradiation DNA repair in *E. coli* mutants, by E. M. Fielden, O. Sapora, and Pamela S. Loverock.
Toxicity of Misonidazole (Ro-07-0582) towards hypoxic cells, by I.J. Stratford.

ELKIND RECOVERY AND "SUB-LETHAL DAMAGE": A MISLEADING ASSOCIATION?

By Tikvah Alper

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A sparing effect of dose fractionation is observed with cells for which survival curves are shouldered. It is common experience that a radiation-free interval will restore to the survivors of prior irradiation the characteristics of the "single-shot" survival curve. This phenomenon, which I shall call "Elkind recovery", is usually called "repair of (or recovery from) sub-lethal damage", the assumption being that a shouldered survival curve signifies a requirement that two or more "sub-lethally damaging" events must accumulate within the cell before it is killed. Elkind recovery, on this view, is a process by which the cell can repair all sub-lethal damage, as long as the final event has not occurred. But the requirement for an accumulation of damaging events is an assumption only, based on shapes of dose-effect curves: there is no supporting experimental evidence.

It would therefore be equally valid to assume, with Powers (1962), that the shoulder to a survival curve represents a dose range within which some incipiently lethal lesions are repaired, but that the cells' repair capacity gradually decreases until the survival curve approaches a final slope determined by the number of unrepaired lesions inflicted per unit dose. Elkind recovery would then be regarded as a process by which repair *capacity* is recovered, perhaps by synthesis of a metabolite essential for that mode of repair.

This model could account for many observations that are difficult to explain within a "multi-hit" or "multi-target" framework—for example, the great variability in survival curve shape as cells in culture proceed through their cycle. Indeed, Sinclair (1973) postulated the existence of "*Q*-factor" as a specific agent of repair that operated to a different extent in different stages of the cell cycle.

If Elkind recovery is regarded as synonymous with "repair of sub-lethal damage", evidence of this repair can be obtained *only* in experiments in which the radiation dose is fractionated. According to a "repair model", on the other hand, the shoulder to the survival curve is itself evidence that repair occurs and that it becomes less effective with increasing dose. To that extent, "multi-hit" or "multi-target" models are inconsistent with "repair models".

The latter would gain in plausibility if evidence could be found that Sinclair's "*Q*-factor" were diffusible not only through the nuclear membrane, but also through the plasma membrane in some circumstances.

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RECOVERY FROM SUB-LETHAL AND POTENTIALLY LETHAL DAMAGE IN TUMOURS

By N. J. McNally

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A comparison has been made of the ability of cells from two different tumours to recover from sub-lethal radiation damage either when left *in situ*, as assayed by regrowth delay, or when excised and assayed for cell survival *in vitro*. Tumours were exposed to a single dose of radiation (D_1) or two doses 24 hours apart (total dose D_2), in each case the tumours being clamped at the time of irradiation. The cell survival assay gave a lower D_2–D_1 than the regrowth assay in each case. For the tumour RIB$_5$C the maximum D_2–D_1 was 8 Gy for cell survival and at least 20 Gy for regrowth delay. For the Fib/T tumour the values were 9 Gy (*in vitro*) and 14 Gy (*in situ*). These *in situ* values, when divided by the oxygen enhancement ratios, are similar to those obtained for normal tissues.

Measurements of tumour control probability in a third tumour ("MT") indicated an hypoxic fraction greater than 80% and a TCD$_{50}$ of 78 Gy. The *in vitro* assay of tumour cell survival indicated an hypoxic fraction of about 5% and a TCD$_5$ of 49 to 56 Gy. These discrepancies can, in part, be reconciled by the observation that the naturally hypoxic, but not the oxic, cells of this tumour were capable of recovery from potentially lethal damage.

EVIDENCE FOR LOCATION OF THE SITE OF ACCUMULATION OF SUB-LETHAL DAMAGE

By P. Bryant and Jane Parker

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Ducane Road, London W12 0HS

Experiments are reported which show that recovery from sub-lethal ionizing radiation damage in *Chlamydomonas* is inhibited by small doses of UV-light at 254 nm. This is in

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agreement with experiments of Han *et al.* (1964) who showed a temporary inhibition of recovery from sub-lethal damage in mouse L-cells. Recovery in this case returned after a period of six hours, presumably due to removal of UV damage by the dark repair system (Rauth, 1967). *Chlamydomonas*, when held in the dark after short exposure to UV light and a first dose of electrons, showed a much reduced capacity to recover from sub-lethal damage inflicted by the dose of electrons. The short exposure to UV light did not alter the survival curve shape obtained with single doses of electrons. Exposure of cells to visible light after the UV light and during the interval between two electron doses allowed recovery from sub-lethal damage to proceed normally. Photoreactivation of cells exposed to UV light is a process specific to the nucleic acids and involves principally the monomerization of pyrimidine dimers formed in the DNA by UV light. On a basis of these data, it is proposed that the accumulation of sub-lethal damage from electron exposure takes place in the DNA and that pyrimidine dimers induced by UV light cause local distortion of the DNA which prevents repair of the sub-lethal lesions. *Chlamydomonas* appears unable to repair UV damage in the dark (Swinton and Hanawalt, 1973a, b); however, photoreactivation enzyme enables cells to monomerize pyrimidine dimers in DNA and thereby removes the block to repair of sub-lethal damage. It is also possible that the molecular distortion engendered by the formation of pyrimidine dimers in the DNA could inhibit the reattachment of DNA to the nuclear membrane following detachment in sub-lethally damaged cells as proposed by Elkind and his colleagues (Elkind and Kamper, 1970).

We conclude from the work reported that the site of accumulation and repair of sub-lethal damage in *Chlamydomonas* is located in or closely associated with the DNA.

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THE QUALITATIVE RECOVERY IN HAEMOPOIETIC STEM CELLS

By R. Schofield

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Damage to haemopoietic tissue can be assessed in humans and most animals only by measurement of blood and recognizable bone marrow elements. In the mouse measurement of the pluripotent stem cell (CFU-S) by a functional assay can be used to assess damage to haemopoietic tissues and subsequent recovery. However, from similar numbers of CFU-S surviving different modes of depletion the recovery will often follow different patterns. Thus measurement of total numbers of CFU-S appears inadequate to describe the haemopoietic status and attempts have been made to study stem cell "quality".

By estimating the number of CFU-S in individual spleen colonies at a standard time (11 days) after injection of normal bone marrow cells into a lethally irradiated mouse, a reproducible profile of CFU-S/colony can be drawn up. When similar profiles are obtained from colonies produced by bone marrow of irradiated or drug-treated mice it is clear that the self-productive ability of the CFU-S may or may not return to normal, *i.e.* there may be a qualitative deficiency in the CFU-S.

Following radiation treatment, both chronic at low dose rate and acute at high dose rate, serial bone marrow transplantation and myleran treatment, both "qualitative" and quantitative recovery is incomplete. On the other hand depletion by isopropyl methane sulphonate (IMS), and probably other cytotoxic drugs, is followed by complete quantitative and qualitative recovery. Similar incomplete recovery is found after transplantation of small amounts of marrow into irradiated mice, whereas full qualitative and quantitative recovery can be achieved with large doses.

STUDIES ON A DNA CONTAINING MATERIAL FROM P388 CELL LYSATES

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In order to study the importance of DNA double-strand breakage and its subsequent rejoining for the survival capacity and chromosome aberration frequency in mammalian cells following radiation treatment, it is of interest to detect changes in the highest molecular weight DNA-containing material that can be isolated from the cell. A number of reports have suggested that double strand breaks can be observed after high doses of X rays, and that, in some cases, a "rejoining" has been observed, characterized by an apparent increase in the sedimentation velocity of particles in a sucrose gradient. In view of the importance of this observation to the interpretation of chromosome breaks and their rejoining and the close correlation between cell survival and these events at the chromosome level, the material from lysed cells sedimented on a sucrose gradient has been studied. A DNA-nucleoprotein material has been observed which is extremely sensitive to low doses of X rays and which is capable of partial reconstitution on incubation following irradiation. The sensitivity and integrity of this complex material is possibly more realistically associated with cell survival than sedimentation studies on DNA alone.

EXTENSIVE AND EQUIVALENT REPAIR IN BOTH RESISTANT AND SENSITIVE *E. COLI* DETERMINED BY A DNA UNWINDING TECHNIQUE

By W. A. Cramp, A. M. George and G. Ahnstrom

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Methods employing "strong" alkali (0.1–0.5 M) to denature cellular DNA (McGrath and Williams, 1966) have at least two associated hazards. Firstly, two types of single strand breaks are exposed with considerable differences of occurrence particularly in oxygenated conditions (Lennartz *et al.*, 1975). Secondly, DNA released by "strong" alkaline lysis has anomalous sedimentation behaviour where properties other than molecular weight play an important role in the sedimentation rate, especially for DNA released from unirradiated cells (Ahnstrom and Erixon, 1973; Young and Smith, 1976). Early work where post-irradiation repair of *E. coli* was measured using "strong" alkaline denaturation also failed to take into account the considerable concurrent degradation of DNA.

We have adopted the strand-unwinding method first described by Ahnstrom and Erixon (1973) using "weak" alkali (0.03 M) to examine radiation-induced strand breakage in the resistant *E. coli* B/r and the sensitive *E. coli* B_{s-1}. Both strains of bacteria showed identical repair characteristics when post-irradiation incubation was at 37°C in non-nutrient saline. The enhancement of the extent of DNA unwinding by the presence of oxygen during irradiation was considerably greater than that of cell killing. When minimal medium was added to the bacterial suspension immediately after irradiation, incubation at 37°C caused a very rapid (2–5 min.) decrease of potential unwinding points. This repair was observed to the same extent in each bacterial strain.

We conclude that the initial and residual strand breaks as measured by the mild alkaline technique do not reflect the survival characteristics of these bacteria.

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THE TIME COURSE OF POST-IRRADIATION DNA REPAIR IN *E. COLI* MUTANTS

By E. M. Fielden, O. Sapora and Pamela S. Loverock

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Clifton Avenue, Sutton, Surrey

The yield of single-strand breaks (ssb) per single-strand genome measured 0.2 sec after irradiation of *E. coli* B/r or Pol. A_1^- with 4.3 MeV electrons was found to be 0.9 breaks/krad in anoxia and 3.2 breaks/krad in the presence of oxygen. By following the increase in the number of breaks due to endo-nuclease action in Pol. A_1^- it was found that 1.3 endonuclease sensitive sites were present for each radiation-induced break. By adding oxygen shortly after anoxic irradiation it was shown that (i) the presence of oxygen is required for full endonuclease activity and (ii) that oxygen is truly dose modifying with respect to the number of radiation-induced breaks and endonuclease sensitive sites.

Paranitroacetophenone (PNAP) increases the yield of single-strand breaks measured 0.2 sec after irradiation of *E coli* B/r to the same extent as does oxygen. Norpseudopelletierine-N-oxyl (NPPN) does not modify the yield of ssb seen. By studying the time course of the enzymatic repair of ssb and DNA "fixed damage" with *E. coli* B/r and K_{12} Pol A_1^- it was shown that neither PNAP or NPPN enhanced the yield of fixed damage of the type produced by oxygen. Repair of radiation-produced ssb in the NPPN experiments was inhibited so that after 120 sec the yield of ssb was the same as was found with PNAP or O_2. It was concluded that PNAP can only mimic one of the effects of oxygen on DNA damage and that NPPN modifies DNA damage in a manner different from oxygen.

TOXICITY OF MISONIDAZOLE (RO-07-0582) TOWARDS HYPOXIC CELLS

By I. J. Stratford

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Misonidazole (Ro-07-0582) is typical of many nitroaromatic and nitroheterocyclic compounds of high electron affinity in its ability to act as a cytotoxic agent specific for hypoxic cells. Chinese hamster V79-379A cells at 37°C exposed to 5mM Misonidazole in hypoxia are reduced to a surviving fraction of 10^{-3} in four hours. In contrast, it takes four days for aerobic cells in this concentration of drug to be reduced to 10^{-3} survival.

For hypoxic cells, plots of cell survival versus contact time with drug show curves which, after an initial shoulder region, are exponential. In an investigation into the factors determining the shape of these survival curves split dose experiments were carried out. These experiments require exposure of cells to drug and hypoxia for a sufficient period to bring survival onto the exponential portion of the survival curve. This is followed by exposure of cells to air before the cells are returned to a hypoxic environment. The interval in air restores the shoulder to the survival curve when the second exposure to drug is given under anaerobic conditions. A recovery curve has been generated. This repair and recovery phenomenon observed after drug damage in hypoxia is unaffected by hyperthermia (41°C).

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

DIAGNOSIS OF SPLENIC TORSION

In a recent article on splenic torsion, Dublin and Rosenquist (1976), demonstrate the feasibility of making a correct pre-operative diagnosis. Radiologically, the patient had a plain film of the abdomen, excretory urography, ultrasound liver spleen scan, an upper GI series, and a coeliac arteriogram. Whether or not barium enema was performed is unknown. At no time is any reference made to the dollar or dosage cost; at no time is there any concern that the patient's clinical presentation merited early surgery. As imaging possibilities have increased in number in our speciality, it seems that making a diagnosis has become more important than managing a patient. I believe this case to be a prime example of that philosophy.

Yours, etc.,
S. S. SCHWARTZ.

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The Hospital of St. Raphael,
New Haven, Connecticut 06511, U.S.A.

REFERENCE

DUBLIN, A. B., and ROSENQUIST, C. J., 1976. Diagnosis of splenic torsion; a combined radiographic approach. *British Journal of Radiology*, *49*, 1045–1046.

In reply

THE EDITOR—SIR,

DIAGNOSIS OF SPLENIC TORSION: A COMBINED RADIOGRAPHIC APPROACH

Dr. Solomon Schwartz recently criticized the multiplicity of examinations employed in making a diagnosis of splenic torsion, as outlined in our paper. The precise clinical diagnosis in our patient, whose clinical condition was relatively stable throughout the period of evaluation, was uncertain. We believe the multiplicity of approach helped to plan the appropriate surgical procedure for this unusual entity. It is appropriate that this comment should be made at this time, particularly in regards to the recent references to the percentage of surgical errors encountered in a variety of practices. It is our opinion that the most precise possible pre-operative diagnosis significantly contributes to the lowering of surgical morbidity and mortality, and is of more than passing academic interest. It is indeed true that in some instances, certain examinations may not be indicated or necessary. However, we do not believe that this is the case in our patient. In addition, it is extremely difficult to put a dollar value on patient morbidity and mortality, a point often overlooked in a criticism of spiralling medical costs.

Yours, etc.,
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Associate Professor of Radiology

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THE EDITOR—SIR,

COMPUTERIZED TOMOGRAPHIC SCAN TERMINOLOGY

Computed tomography, the simple terminology suggested by Professor Isherwood (1977), only describes the computer-assisted act of recording scans, to the exclusion of subsequent medical studies.

An additional, more comprehensive term is therefore needed, also to signify the clinical importance and multidisciplinary impact of this young technology, which already has stamped its mark on radiodiagnostic procedures, radiotherapy-planning, neurological investigations, anatomical teaching and medical thinking as a whole.

The term coined for this new discipline is Tomology which, etymologically, means "the study and science of body (or brain) sections".

Yours, etc.,
JAN DE WINTER.

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REFERENCE

ISHERWOOD, I., 1977. Computerized tomographic scan-terminology. *British Journal of Radiology*, *50*, 374.

THE EDITOR—SIR,

SI PREFIXES

In response to the several letters published in the *British Journal of Radiology* recently regarding SI prefixes, I am forced to make comment. The introduction of SI units into medicine has met with considerable resistance, as in other fields. However the reason for overcoming this resistance is, surely, to achieve some degree of international standardization. Although the Americans appear to be especially reluctant, there is no good reason for delaying the introduction of SI wherever possible as soon as possible.

Surely the recommended prefixes cover all the eventualities which might be met in medicine? The example given by A. Feldman, "0.130 E+05 Bq" should be written "13 kBq".

This notation is well documented and can thus be interpreted by anyone reading the paper in which it is written—whether or not they are versed in the subject jargon!

Yours, etc.,
M. F. DOCKER.

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REFERENCE

FELDMAN, A., 1977. SI Prefixes. *British Journal of Radiology*, *50*, 296.

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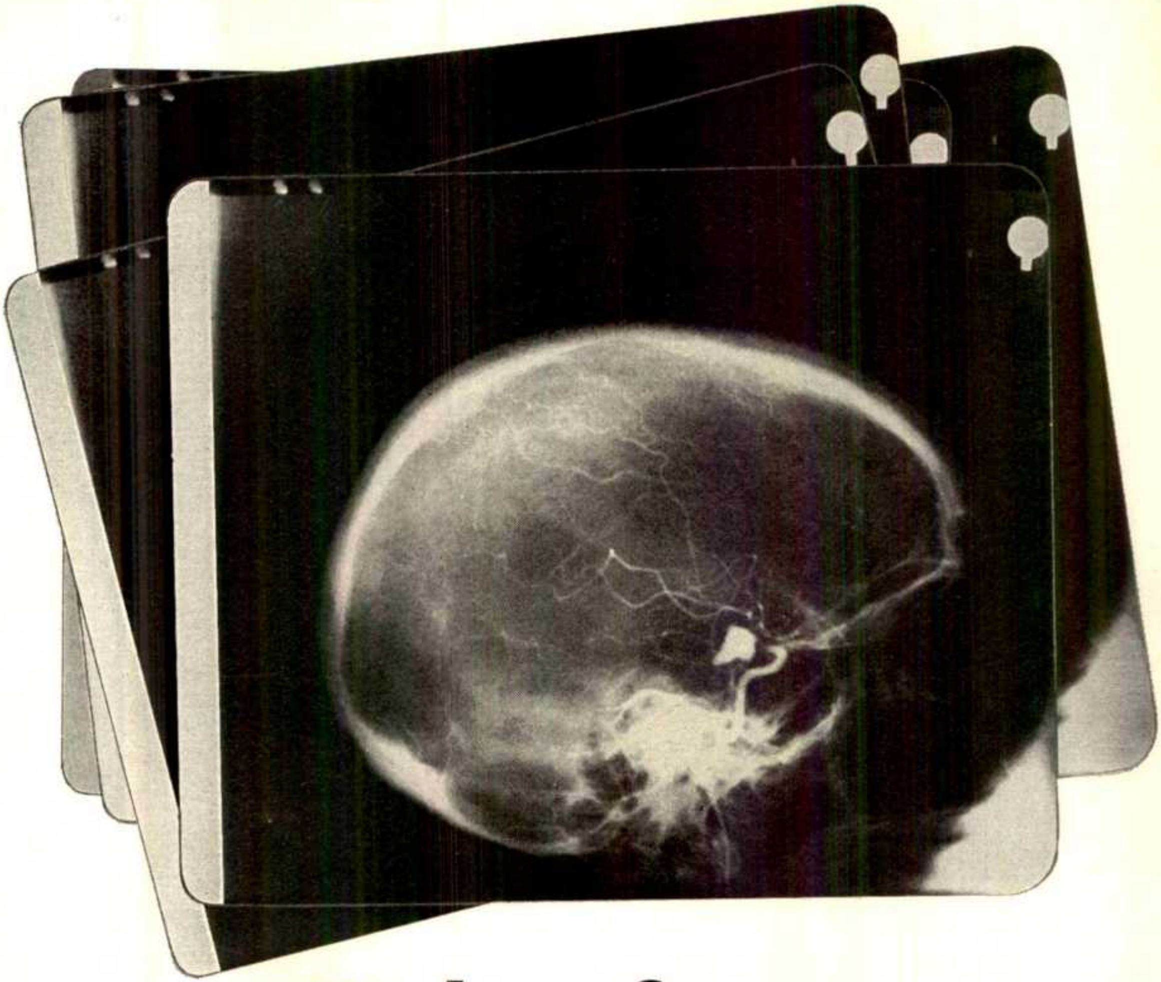

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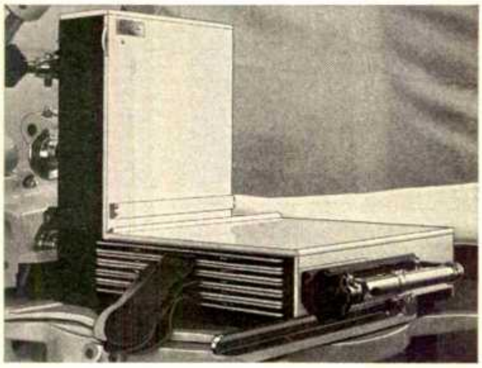

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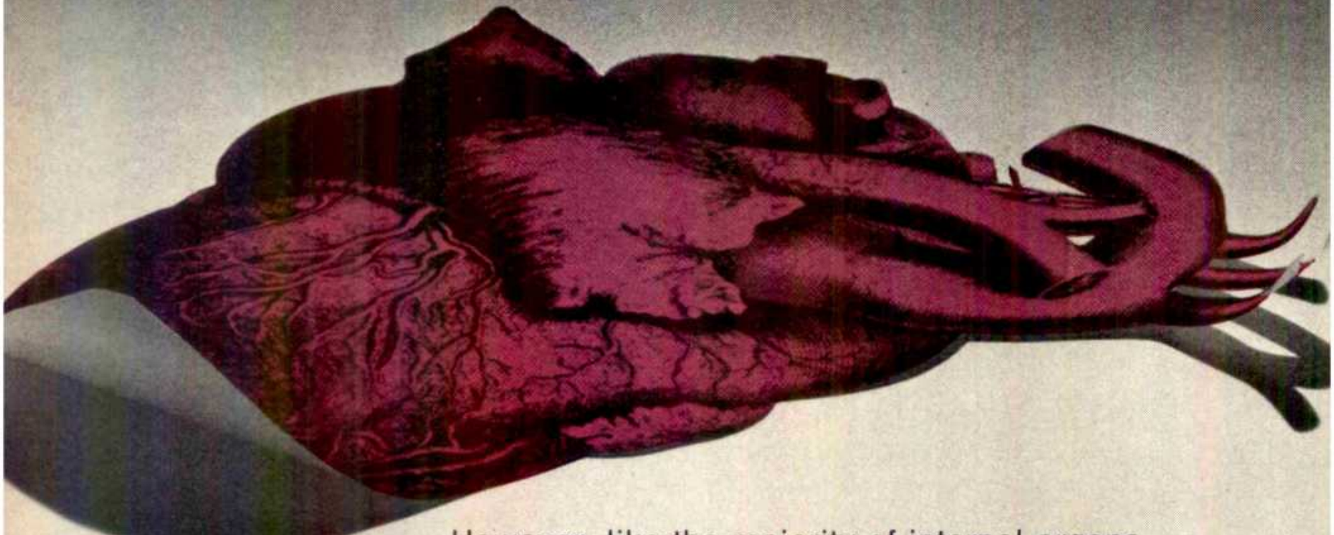

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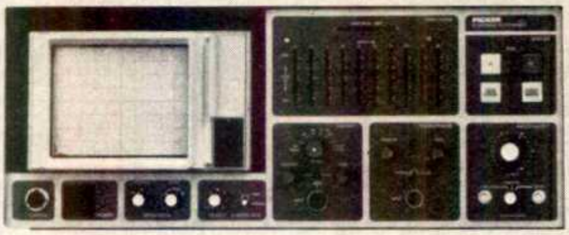

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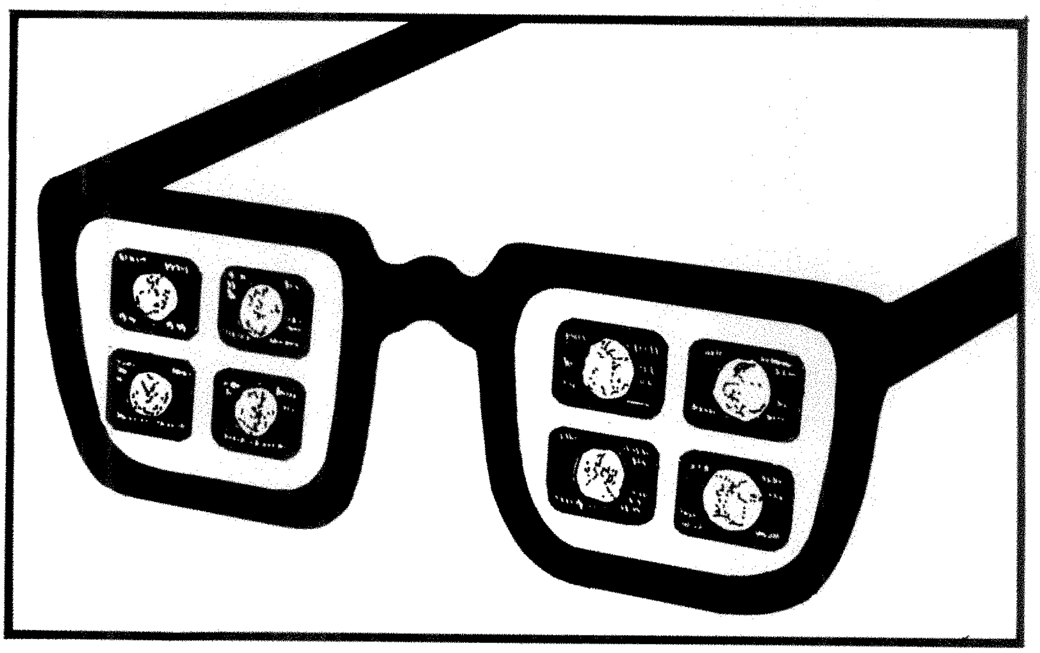

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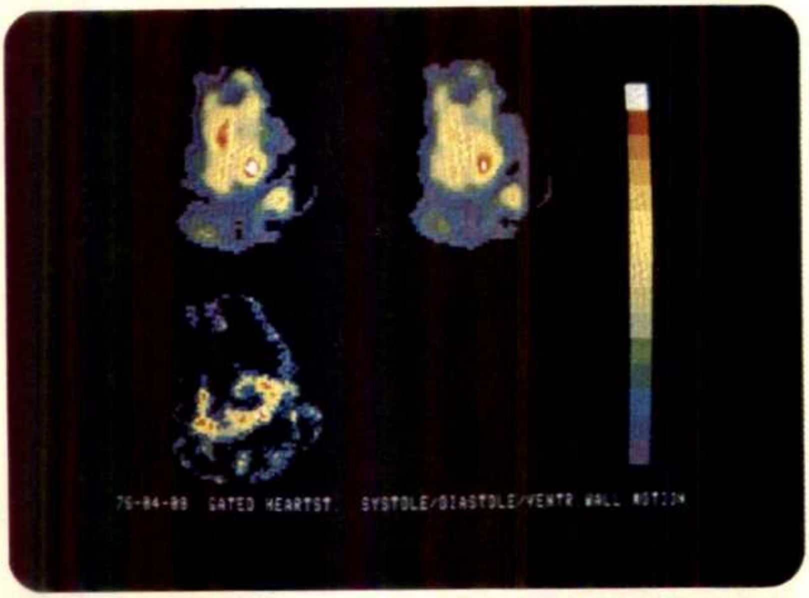

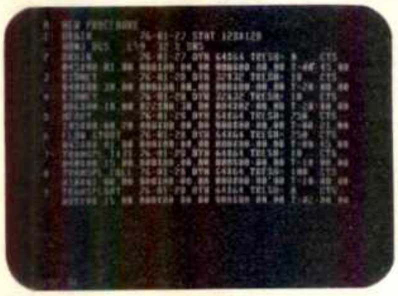

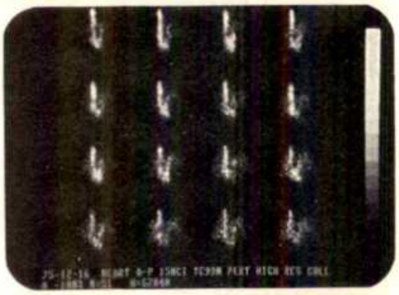

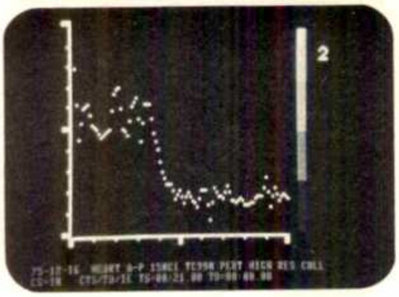

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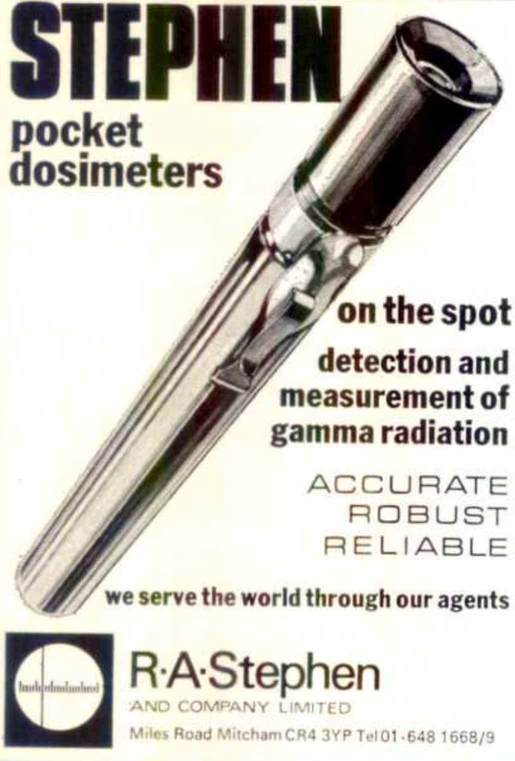

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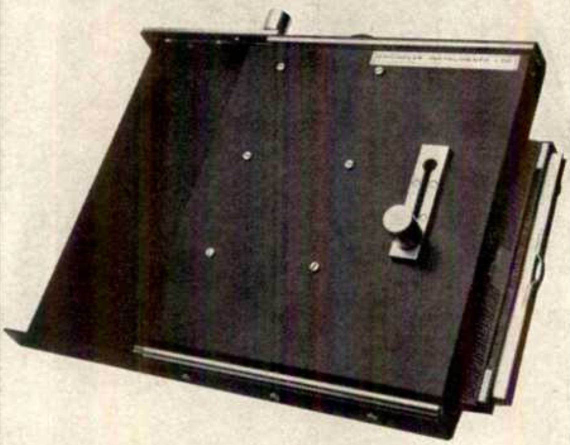

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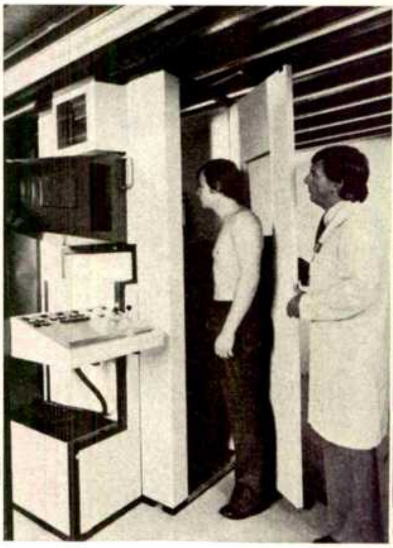

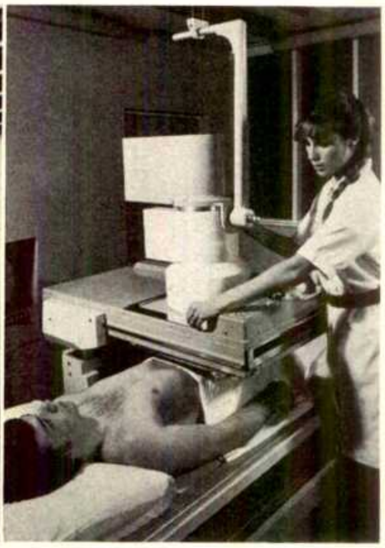

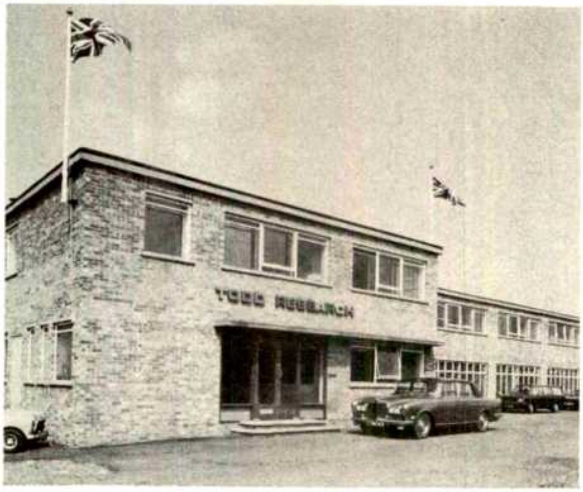

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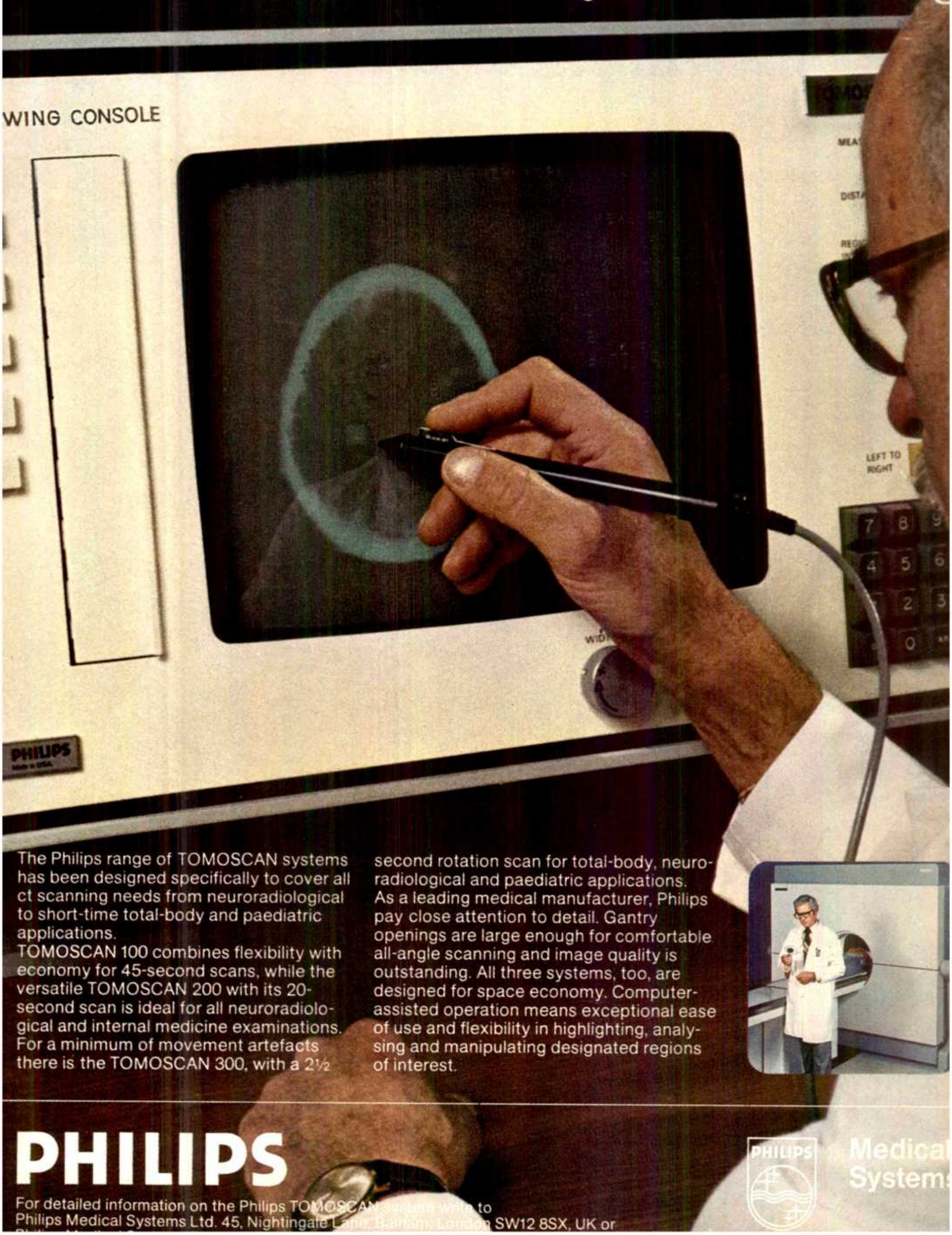

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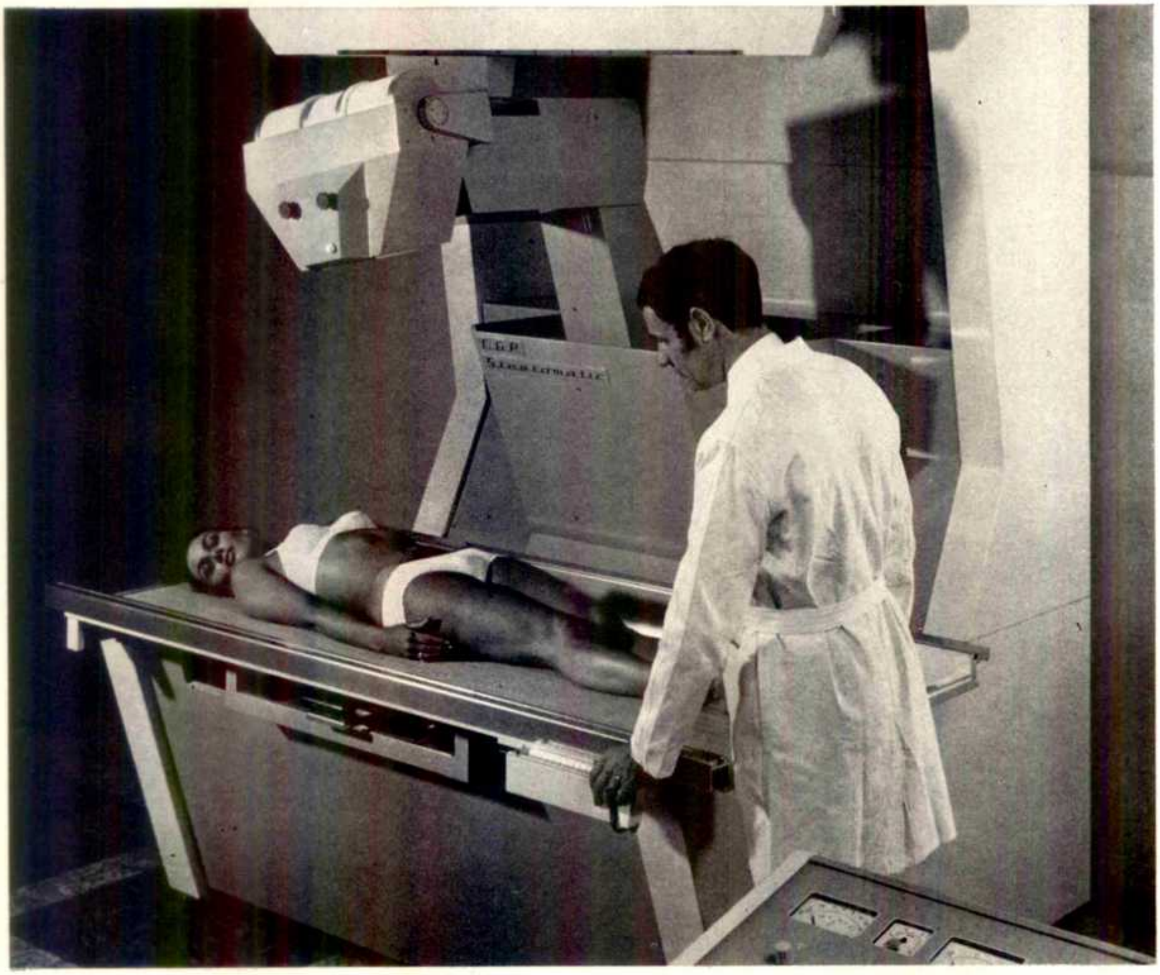

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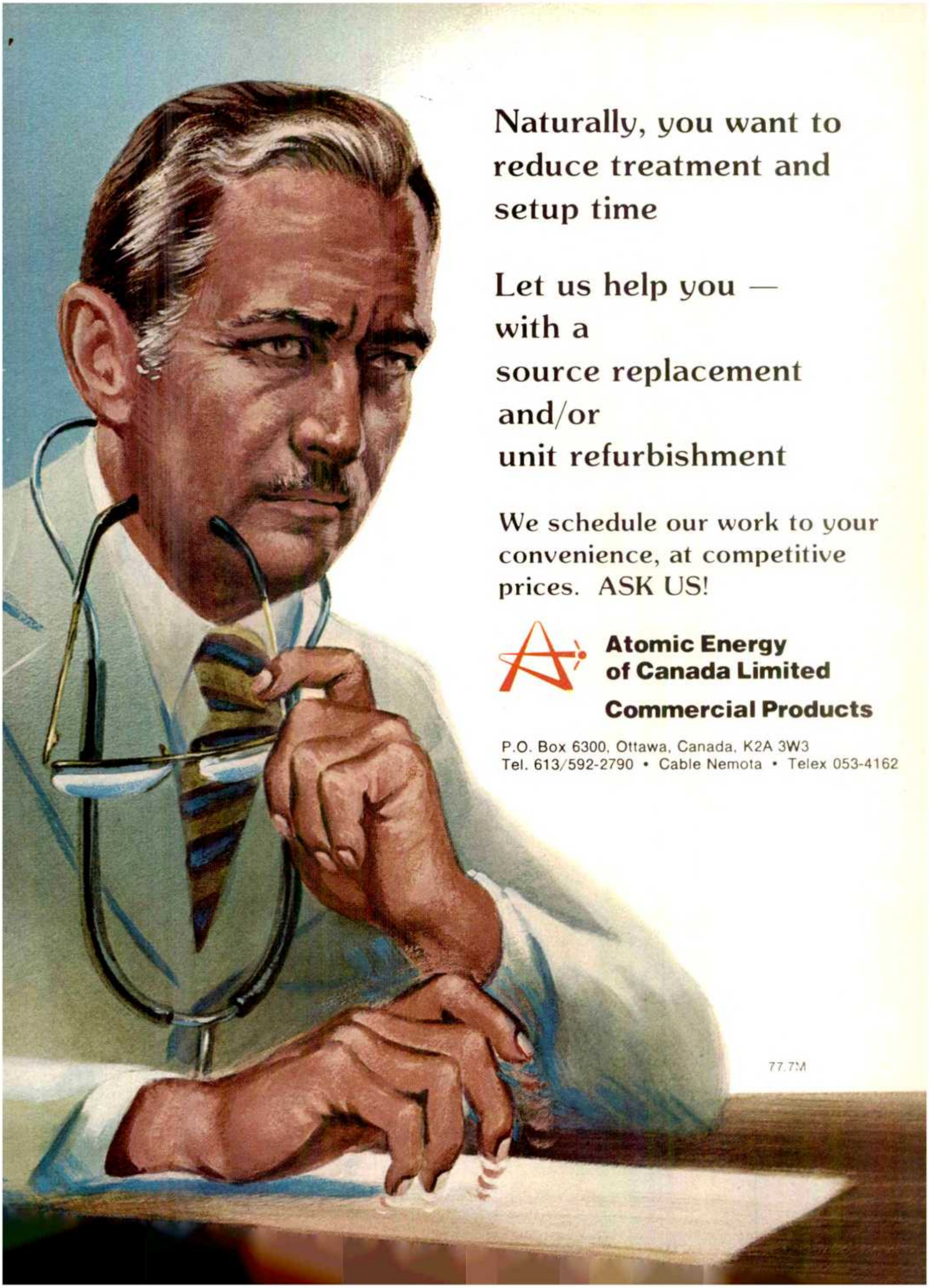

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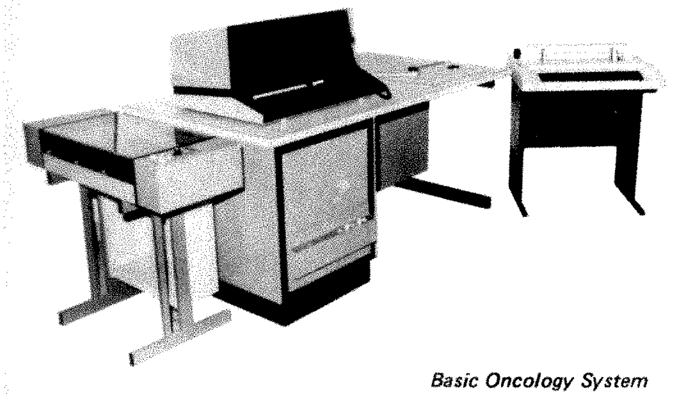

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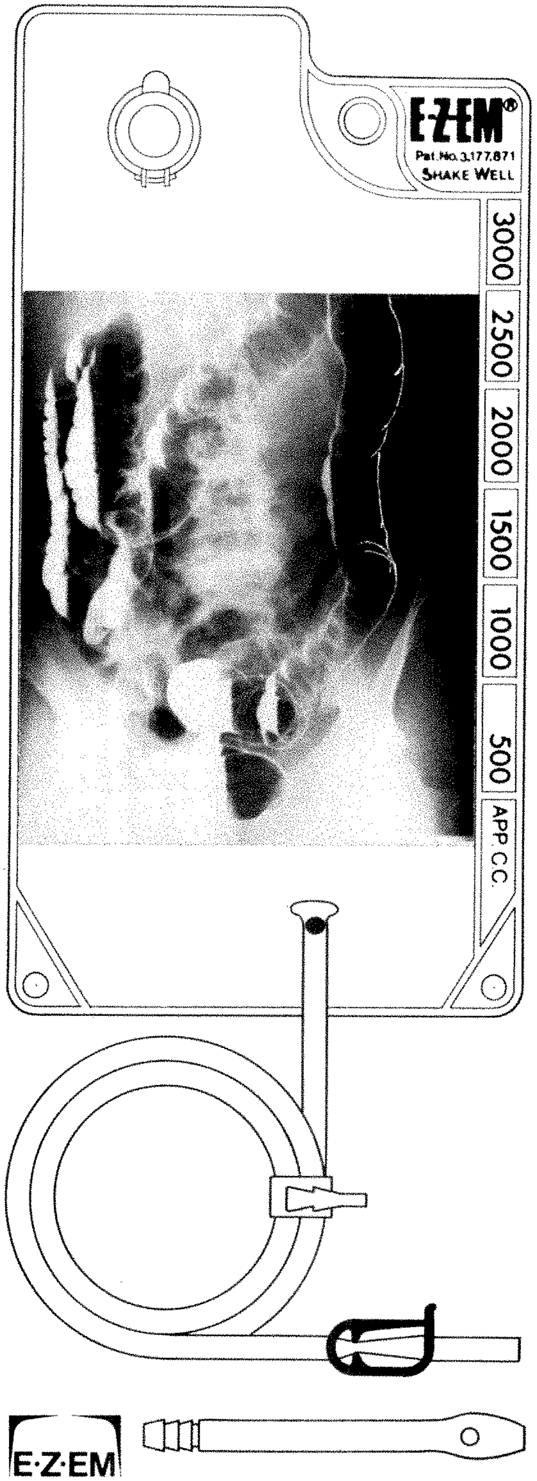

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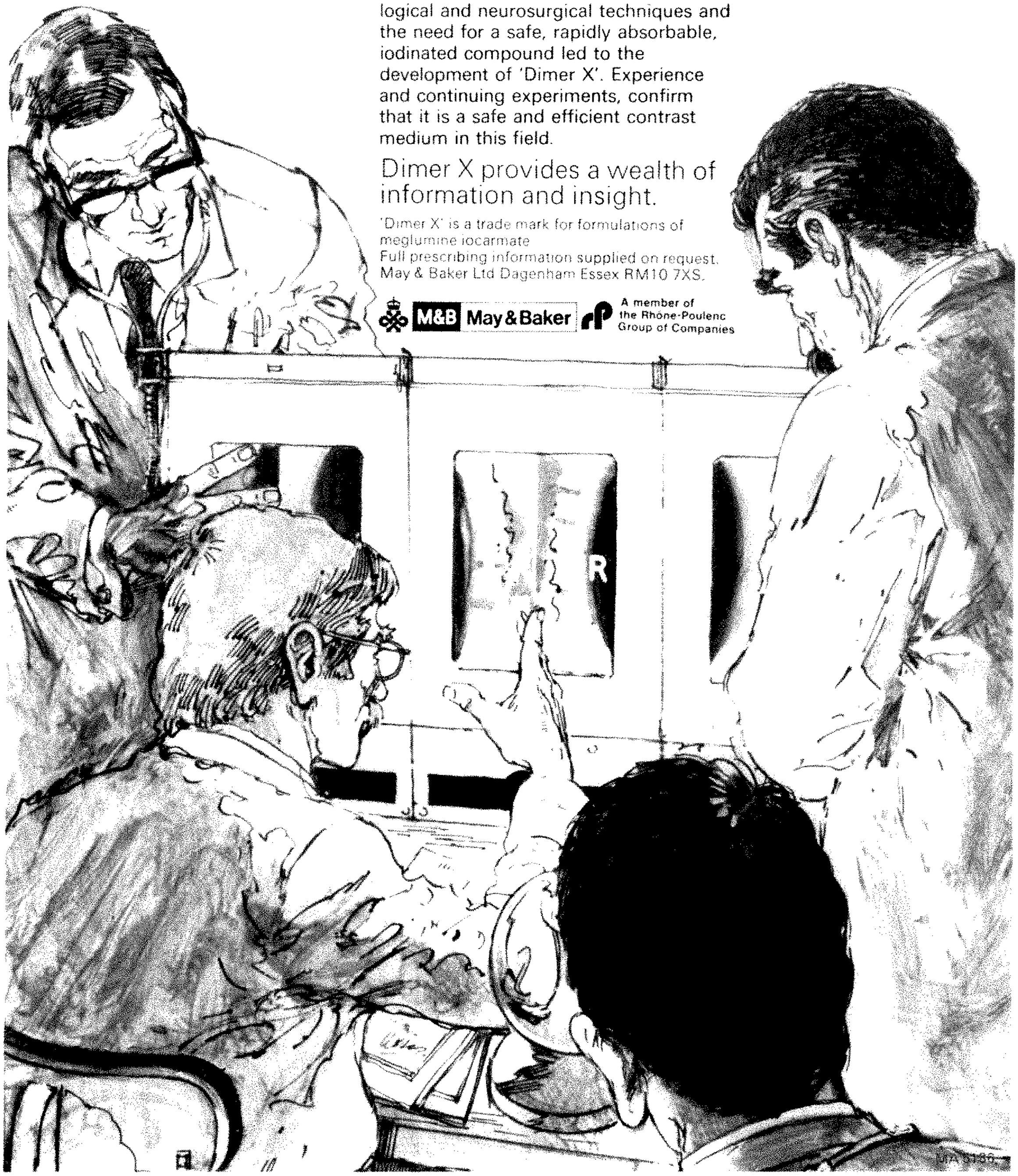

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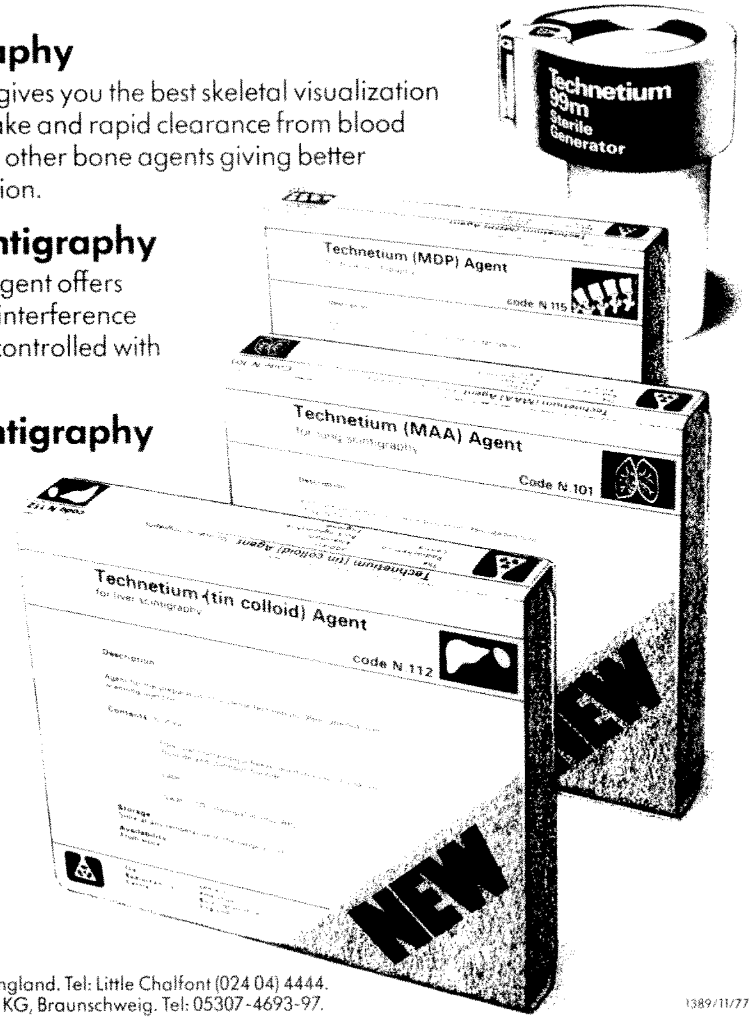

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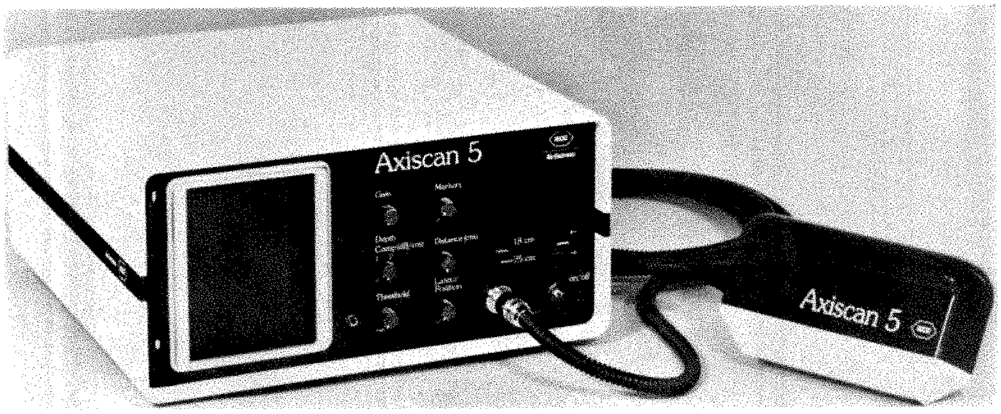

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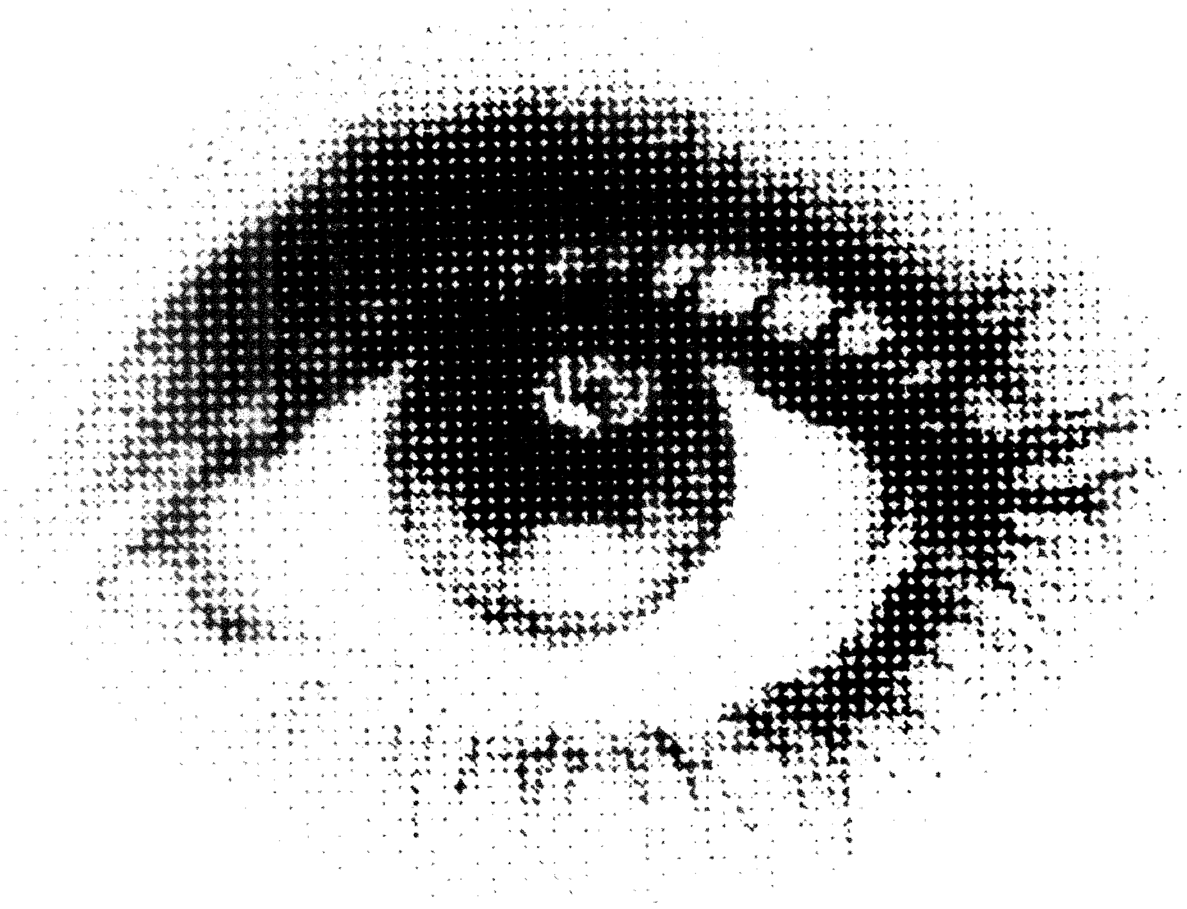

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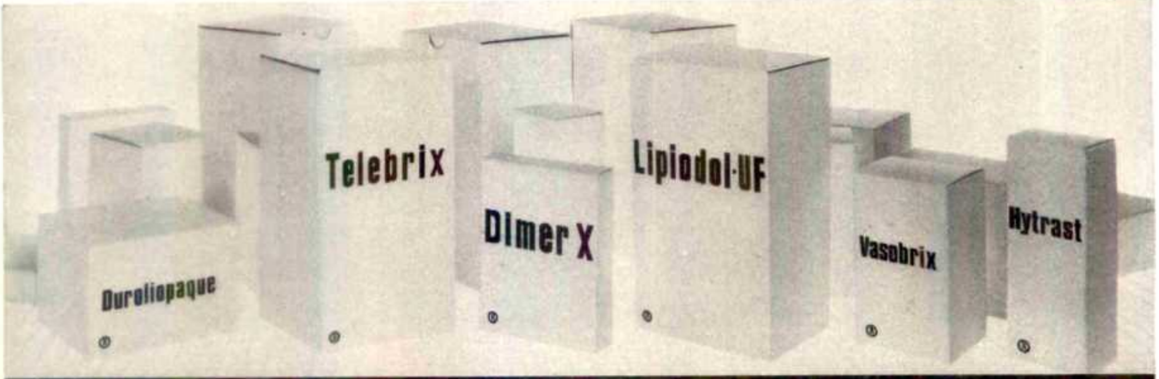

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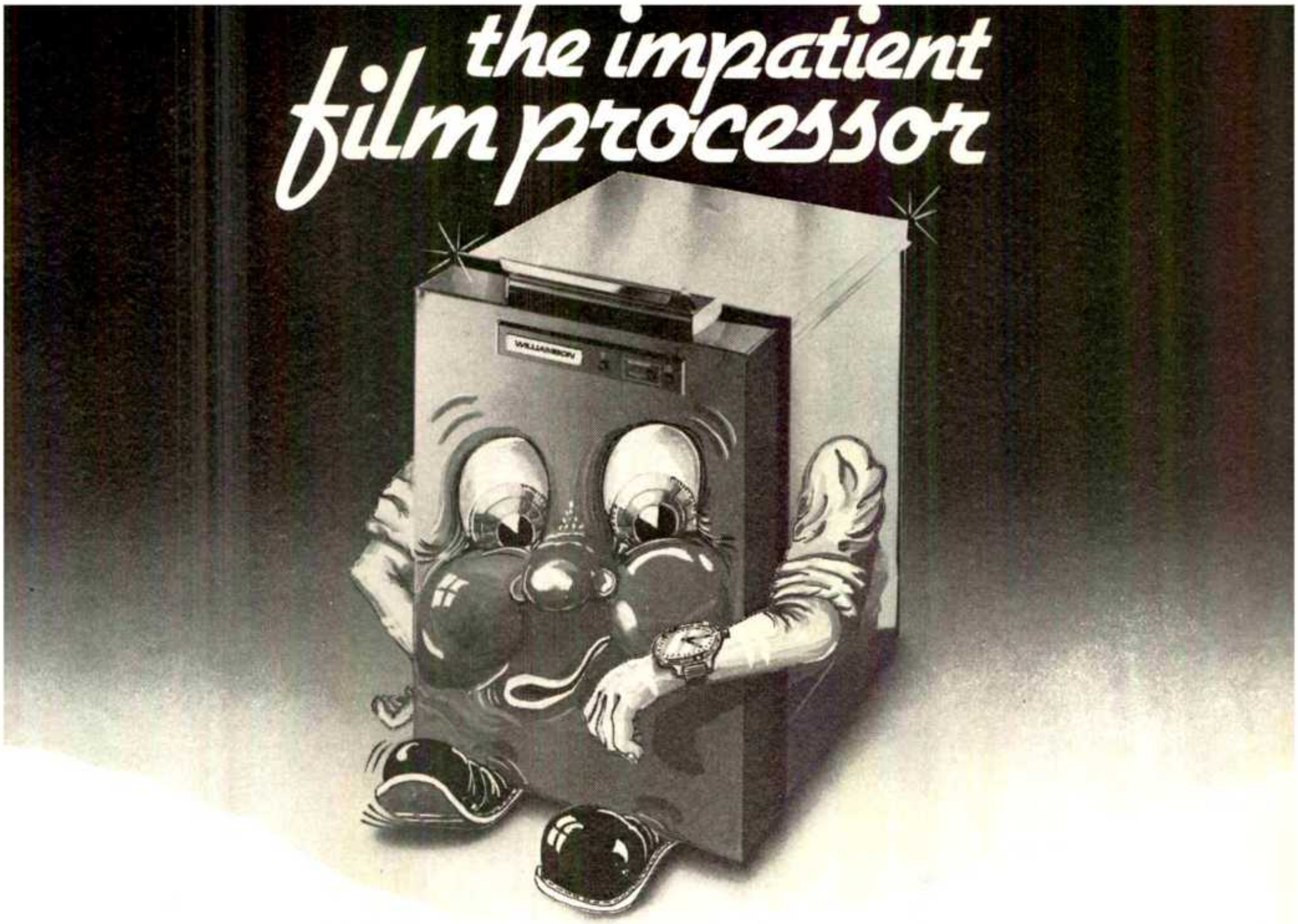

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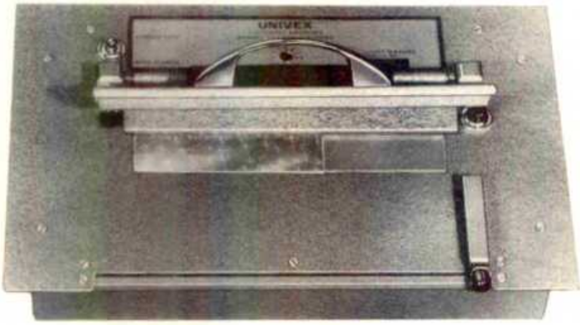

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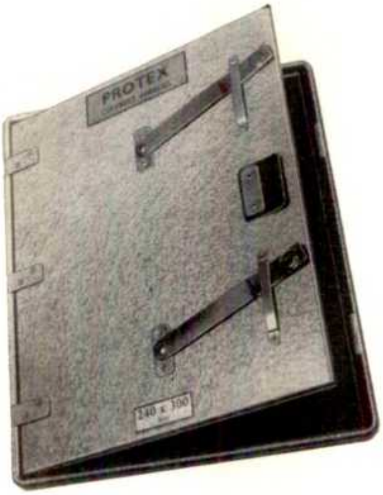

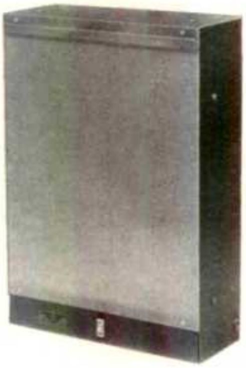

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The association between vesico-ureteric reflux and renal damage has been recognized for some time, but it has usually been assumed that the damage is due to infection promoted by the reflux. However, observations by Rolleston and his colleagues in New Zealand have indicated a link between the severity of reflux and renal damage. Furthermore they have suggested that reflux penetrating into the renal substance is the factor most likely to explain the production of renal scarring.

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VOLUME 50 NUMBER 600 DECEMBER 1977

The British Journal of Radiology

Improvement in the computer-assisted diagnosis of cerebral tumours

By G. H. du Boulay, F.R.C.P., F.R.C.R., D. Teather, M.Sc.,[*] D. Harling, B.Sc.[†] and G. Clarke[‡]

Lysholm Radiological Department, The National Hospital, Queen Square, London WC1N 3BG and Department of Computer Science, The City University, St. John Street, London, EC1

ABSTRACT

Most applications of Bayes theorem in computer-aided diagnosis have been to situations involving the differential diagnosis of a small list of disease categories. In the case of the diagnosis of cerebral tumours, if each tumour type in each main anatomical situation is counted as a single diagnosis, there are about 100 possible disease categories. This paper investigates a method of incorporating expert prior information into the computer-aided diagnosis process so that this large number of categories can be handled.

We consider the problem of differentiating between a number of similar diseases $D_1 \ldots D_k$ based on information from a set of n possible symptoms or signs. Suppose the clinician observes a patient with symptom pattern $S_1\bar{S}_2S_3 \ldots S_n$, where S_j denotes the presence, $\bar{S}_j$ the absence of the jth sign. The conditional probability $P\ (D_i\ S_1\bar{S}_2S_3 \ldots S_n)$ then provides a valuable aid to diagnosis since this specifies the likelihood that this patient has disease D_i.[‖]

One method of dealing with the data mathematically is by using Bayes theorem. Bayes theorem gives:

$$P(D_i \mid S_1\bar{S}_2S_3 \ldots S_n) \text{ is proportional to } P(S_1\bar{S}_2S_3 \ldots S_nD_i)\ P(D_i)$$

(The probability of disease i given the presence of symptoms S_1 etc. is proportional to the probability of the symptoms S_1 given disease D_i times the probability of disease i in the population.)

Common practice (de Dombal *et al.*, 1975; Knill-Jones, 1975) is to assume that the symptoms are independent within each disease (that is to say that within each disease category the incidence of one symptom is not affected by the occurrence of another so that the probability $P\ (S_1\bar{S}_2S_3 \ldots S_nD_i)$ may be calculated using

$$P\ (S_1\bar{S}_2S_3 \ldots S_nD_i) = P\ (S_1 \mid D_i)\ P\ (\bar{S}_2 \mid D_i) \ldots P(S_nD_i)$$

where $P\ (\bar{S}_j \mid D_i) = 1 - P\ (S_j \mid D_i)$.

The diagnostic process is then based only on a list of prior incidences $P(D_i)$ and a table or matrix giving the incidence of each sign in each disease category, viz. $P(S_j \mid D_i)$ with $j = 1 \ldots n$, $i = 1 \ldots k$.

The probabilities $P(S_j \mid D_i)$ have to be estimated from a data base of past patient records.

Typically this probability is estimated by the observed frequency

$$f_{ji} = \frac{M_{ji}}{(M_{ji} + N_{ji})} \quad . \quad . \quad (1)$$

where M_{ji} is the number of cases of disease i in which the jth sign was present, N_{ji} is the number of cases of disease i in which the jth sign was absent.

If the number of disease categories is large a typical data base of between 500 and 1000 cases may provide only one or two cases in some disease categories. The estimates P_{ji} so obtained may be quite unreliable and the diagnosis obtained using Bayes theorem of little or no value.

PRIOR INFORMATION

In situations in which the number of disease categories is very large the diagnostic categories may be a precise description of the physiological or anatomical defect. In this case the expert clinician may have considerable prior information from experience as to which signs are likely to be present in patients in any one disease category.

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[*] School of Mathematics, Computing and Statistics, Leicester Polytechnic, P.O. Box 143, Leicester.

[†] The Computer Centre, University of Hull.

[‡] Computer Science, The Polytechnic of North London, London, N7.

[‖] (The notation in this sentence means the probability (P) of Disease i (D_i) *given* the presence of the symptom pattern S_1 and $\bar{S}_2$ and S_3 up to S_n.)

Clearly the clinicians prior information may be more precise about certain symptom disease combinations and the form of the prior estimate should reflect this fact. Thus we seek a prior estimate of the probability of a particular symptom in a particular disease $P(S_j\ D_i)$ and we may do it by using a mathematical formula

$$P_{ji} = \frac{a_{ji}}{(a_{ji}+b_{ji})} \qquad . \quad . \quad (2)$$

where a_{ji} and b_{ji} can be thought of as the number of hypothetical cases of disease i with and without the symptom j.

This is similar in form to the observed frequency estimate (1) and large values for $(a_{ji}+b_{ji})$ are used to indicate that the clinician's prior estimate P_{ji} is precise. For instance, the clinician estimates a probability, .9 for the jth symptom in the ith disease. He further estimates his precision as high and therefore gives $a_{ji}+b_{ji}$ the value of 10.

To keep the correct proportion of positive and negative cases a_{ji} must equal 9 and b_{ji} equal 1, thus—

$$P_{ji} = .9 = \frac{9}{9+1}$$

This prior estimate may be combined with the data base to give a new estimate as—

$$\frac{M_{ji}+a_{ji}}{M_{ji}+a_{ji}+N_{ji}+b_{ji}}$$

(For justification of this combination see for example Aitchison and Dunsmore, 1975.)

The above formula indicates that a_{ji}, b_{ji} have the effect of introducing the equivalent of $(a_{ji}+b_{ji})$ "new" or "invented" cases into the data base. Hopefully this combination of invented and observed data should produce more reasonable probability estimates than that based on the rather scanty data base of past patient records.

THE TUMOUR DATA

In a previous paper du Boulay and Price (1968) describe the establishment of a suitable data base for use in computer-aided diagnosis and the use of a simple weighted scoring technique to produce a computer diagnosis. As in the previous work, we divide the cerebral tumours into three groups and apply various diagnostic methods to each group separately.

Table I shows the number of disease categories in each group. 500 signs are potentially available in making a "computer" diagnosis. In the application of Bayes theorem assuming independence there are in excess of 78 000 probabilities to be estimated. The data base comprised only some 700 cases. There is an obvious need to supplement this sparse past data with the clinicians prior judgments. To ease the assessment of such a large number of probabilities the clinician (G. duB) was requested to estimate the likelihood of a positive result for each sign in each disease simply on a scale of five probabilities, .1, .3, .5, .7 or .9). The accuracy of each assessment was also estimated on a scale of 3 (very accurate, accurate, inaccurate). This information was then used to produce the data of invented positive and negative cases a_{ji}, b_{ji} respectively. Typically $(a_{ji}+b_{ji})$ took values between 1 (inaccurate) and 10 (very accurate) having the effect of roughly doubling the number of cases used in the estimation of the probabilities.

TABLE I

	Group 1	Group 2	Group 3
No. of disease	16	99	47

A computer program was written to combine these invented cases with the existing data set and to produce the required probability estimates. A second program was written to utilize these estimates via Bayes theorem to calculate the disease probability for any new patient whose sympton profile was available.

DIAGNOSIS OF TEST CASES

The estimated probabilities have been used in Bayes theorem to produce diagnoses on a short series of prospective cases not included in the original data set.

The accuracy of the simple weighted scoring technique (du Boulay and Price, 1968) has been compared with the above Bayesian technique. They have also been compared with the radiologist's diagnosis unaided by computer (but with the help of extra clinical information). The results are described for each disease group separately.

Group 1 Cases. All the tumours in Group 1 lie within a very restricted area, just above and to the side of the sella turcica. All, or almost all, can extend into any part of this small space, though there is a tendency for some to be principally above and behind and others above and in front, while parasellar extension of some is much more common than it is of others. Thus the exact localization of the mass, though important in explaining the symptoms and planning treatment, is difficult to use in distinguishing one type of tumour from another. Nevertheless, in this work we have principally tested the predictions of pathological type of tumour from a knowledge of its exact position by restricting ourselves to plain X-rays and to pneumoencephalography.

Group 1 consists of nine different types of tumour and because some of these can occur above and/or to the side of the sella, or in the case of metastases can, in addition, be multiple and scattered elsewhere in the head, and because each tumour type with its position is treated as a unique diagnosis, there are 16 disease categories in Group 1.

The intention was not to present necessarily fully worked up cases, but to test some in whom only a restricted diagnostic regime had so far been employed. None of the test cases had had an angiogram.

In this small group therefore the computer's calculations were based upon the presence or absence of 93 different indicants (symptoms) read from a set of plain X rays, plus 90 indicants (symptoms) from a pneumoencephalogram (or in one case a ventriculogram).

In spite of the large number of indicants investigated (183) the nine patients gave rise to only eight positive indicants on plain X ray and 14 on pneumoencephalography.

The nine cases proved at operation to be:

Chromophobe adenoma	4
Eosinophil	1
Meningioma	2
Craniopharyngioma	2

One of the chromophobe adenomas extended into the parasellar region; the other three did not.

The correct diagnoses together with the computer's predictions are compared with the radiologists' opinions in Table II.

Pituitary Adenomas

In three of the chromophobe adenomas the predictions of both computer and radiologists coincided exactly, and were correct.

It should be noted in:

Case 2—(a supra- and parasellar tumour) that since a supra- and a parasellar tumour are treated as separate diagnoses in the program, their combined probabilities cannot total more than 1.0. The computer has divided the probabilities on the basis of both the prevalence of parasellar extension within the material and the symptoms.

Case 4—This was a purely intrasellar chromophobe with a normal pneumoencephalogram. The diagnosis of intrasellar chromophobe does not figure in the program, so all that the computer can do if chromophobe heads the list of likely diagnoses is to aportion its predictions between the two available positions, supra- and parasellar, again more or less in proportion to their prevalence in the material.

Case 5—an eosinophil adenoma with suprasellar extension. There are only one or two eosinophil adenomas on the file. The computer predicted a chromophobe on the basis of frequency and because the skull, apart from the sella turcica, was normal, but the radiologists knew that the patient had acromegaly. Both radiologists and computer correctly excluded a parasellar extension of the mass.

Craniopharyngioma

Case 8—a craniopharyngioma. Radiologists and computer assessed this as the second most likely diagnosis. The radiologists preferred a diagnosis of meningioma and the computer, by a narrow margin, predicted a suprasellar chromophobe adenoma.

Group 2 Cases. The data in Group 2 cases are managed in the same way, but there are differences in the potential difficulties and in the advantages of reaching a precise diagnosis. For one thing the number of possible diagnoses is 99 not 16, and for another a knowledge of location of the tumour is as important for the management of the patient as is a correct decision about its type.

Notwithstanding the fact that location and type are indissolubly mixed in the computations by the nature of the disease categories used, the success has been examined in two parts, comparing the radiologists, the original scoring technique and the new technique's performance first on the question of tumour position (Table III) and secondly on its nature (Table IV).

The number of investigations employed on the 16 patients of the test group was not so limited as in Group 1; in most the regime might be described as full in that we used every test that was thought desirable.

More indicants are therefore potentially involved, but in the event the mixture of plain X rays, carotid angiography, pneumoencephalography and scintigraphy only provided a total of about 30 positive indicants in their various combinations.

Tumour Position. In the disease index 21 alternative topographic situations are offered. Radiologists without any mathematical aid have little difficulty in predicting where the tumour will be found (though they do have difficulty in knowing the furthest edge of the tumour's territory). In 11 of the 16 cases the radiologists were right in their first choice, and in only two did they clearly state a location which was wrong without giving the correct location as a second

TABLE II

Group I cases

		Computer predictions		Radiologists' predictions	
Case No.	Final diagnosis	Correct diagnosis probability given by computer	Alternative diagnosis if given significant probability	Concordance (+) with computer	Difference from computer
1	Suprasellar chromophobe adenoma Parasellar extension (none)	0.92 0.07	+	+ +	
2	Suprasellar chromophobe adenoma Parasellar extension (present)	0.63 0.37		+ +	
3	Suprasellar chromophobe adenoma Parasellar extension (none)	0.52 0.003	Meningioma 0.17 Glioma 0.15	+ +	
4	Intrasellar chromophobe		Suprasellar chromophobe adenoma 0.68 Parasellar extension 0.32	—	Intrasellar chromophobe adenoma
5	Suprasellar eosinophil adenoma Parasellar extension (none)		Suprasellar chromophobe adenoma 0.92 Parasellar extension 0.07	— +	Suprasellar eosinophil adenoma
6	Meningioma		Craniopharyngioma 0.62 Suprasellar chromophobe adenoma 0.36	+	
7	Meningioma	0.76		+	
8	Craniopharyngioma	0.41	Suprasellar chromophobe adenoma 0.54	—	Meningioma (craniopharyngioma as 2nd choice)
9	Craniopharyngioma	0.999		+	

TABLE III

Group 2 Cases—Tumour Position

	Prediction correct as choice						
	1	2	3	4	5	6	Other
Radiologists with clinical help	11	2					3
Old weighted score technique	4	1	3		3		5
New method	9	1	1	1	1	1	2

alternative. In one further equivocal case they were probably wrong.

The simple weighted scoring technique was nowhere as good as the radiologists, though it did place half the tumours correctly within the first three choices.

The new Bayesian technique, by which the position of nine have been correctly predicted as first choice and one each as second and third choice, is very much more satisfactory.

Tumour Type. In the disease index 14 different pathologies are given. The test group contained between five and seven of these. It has not been

TABLE IV

GROUP 2 CASES—TUMOUR TYPE

	Prediction correct as choice							No prediction	Success unproved
	1	2	3	4	5	6	Other		
Radiologists with clinical help	6	3					3	4	
Old weighted score technique	1	1	3	1	2	1	3		4
New method	7	4	1						4

possible to establish the tumour type unequivocally in all the test cases, even within the relatively broad categories of the simple disease index used, in spite of biopsy or autopsy.

Of 12 unequivocally known results the radiologists unaided recognized six as first choice and three as second choice. In three they were either unable to suggest the pathology or were wrong. In the other four cases they were also unable to make any suggestion of the tumour type, or made one which was clearly erroneous. Radiologists, therefore, were far less successful at predicting tumour type than they were situation.

The original scoring technique was very bad; the results were no better than random.

By contrast the new technique was shown to have performed considerably better than the radiologists, placing seven tumours in the correct category as first choice and all 12 within the first three choices. Some, but not all, of the tumours with equivocal biopsies were probably also correctly predicted.

Group 3 Cases. It was impossible to compare the performance of the new with the old techniques because the original list of X-ray signs pertaining to vertebral angiography had been so updated that all the earlier material was inappropriate and had been erased from the file.

The project undertaken was designed therefore to show up the weakness of the material related to the newly written list of vertebral angiogram indicants. The two halves of the diagnosis (site and pathology) were not examined separately. An error in either half invalidated the whole.

A comparison was made between (1) the computer's predictions based only on the vertebral angiograms, (2) the final proved result of operation or autopsy, and (3) the radiological opinion (which, as usual, was written with knowledge of the clinical presentation and other radiological tests and after full discussion).

Twenty cases were used. From a possible total of 41 disease categories there were actually examples of nine in the test group. The large number of possible indicants (113), which may, in this program, be read from a vertebral angiogram, and the very small amount of proven material on file so far was unpromising and, as expected, some ridiculous mistakes were made using the new technique, probably because of the high proportion of certain types of tumour in the test group.

In each case the eight most probable diagnoses were printed in order, along with probability figures. Ten (half the cases) were predicted correctly within the first three choices.

Of the 20 cases there were only three in whom the true diagnosis did not figure somewhere in the eight listed predictions, and of these one was a mistake only in the number of haemangioblastomas (single mistaken for multiple).

The Radiologists' Success

In 12 of the 20 cases the radiologists achieved a full correct diagnosis in the report on the vertebral angiogram. In six cases they correctly recognised the probability of, for instance, a cerebellar, brainstem or extra axial mass, but were either unwilling to predict the pathology or occasionally predicted it wrongly (meningioma for chordoma). In two cases the reports were too vague to give any guidance other than the general probability of a posterior fossa mass.

It has to be emphasised that when the reports were written the radiologists were in possession of the results of other tests and had been given the clinical opinion. When the vertebral angiograms were reviewed by one radiologist alone (G. duB), without any clinical or other radiological data, his diagnostic success was not nearly so high, difficulty being experienced in distinguishing intra-axial from extra-axial cerebello-pontine angle masses and, even, between brainstem and cerebellar tumours. In general terms radiologists, with all available data, could not draw distinctions between metastases and gliomas and between different kinds of extra-axial mass.

CONCLUSIONS

What can we conclude from the small series of Group 1 patients? It seems at least in this small series that the computer has been successfully programmed to match the diagnostic accuracy achieved by the radiologists, even though they are working as a combined team and have clinical information available. Possibly the program reflects and conforms to the radiologists' diagnostic method. Perhaps it indicates the possibility of transmitting experience to a less expert team.

In Group 2 the success of the program in recognising tumour type is better than the radiologists' performance and this presumably indicates that the radiologists were misled by the information that they used—perhaps the clinical findings—or did not understand the significance (or lack of significance) of some of the radiological signs.

Group 3 cases were tested in relation to vertebral angiography alone. The results seem less encouraging, but this raises the possibility that vertebral angiography without other supporting clinical evidence or radiological tests is fallible.

FUTURE WORK

It seems that the computer may be a valuable aid to diagnosis. More important is its potential in choosing the best investigation to carry out. At present we are investigating a mathematical method of calculating the best investigation based upon both the historical data and the experts' assumed probabilities.

Hopefully, also, it will enable us to isolate the most important indicants (that is to say radiological signs). It was very striking how few such signs were actually used of the available 500 in the present work.

Computed tomography has revolutionized the diagnosis of Group 2 and Group 3 cases since this work was first undertaken, and it will be important to incorporate C.T. scanning so that relevant choices of investigation can be calculated.

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Comparison of ultrasound and computer-assisted tomography in pancreatic diagnosis

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ABSTRACT

In a series of patients suspected of having pancreatic disease both ultrasound and computerized tomography (CT) were performed. The diagnosis has been confirmed in 50 patients. Computerized tomography visualized the pancreas in all 50 (100%) whereas ultrasound was successful in 40 patients (80%). The ultrasound failures were due to bowel gas anterior to the pancreas.

The overall diagnostic accuracy was 84% for computerized tomography and 64% for ultrasound; however, in those cases where ultrasound successfully detected the pancreas the diagnostic accuracy was 80%.

Computerized tomography (CT) and grey scale ultrasound are important developments in pancreatic imaging (Haber *et al.*, 1976; Sagel *et al.*, 1976). Both CT and ultrasound produce a two-dimensional image of a thin slice of a patient, the thickness of the slice obtained by both techniques is approximately 1 cm. CT utilizes X-radiation and scanning is performed by an automatic mechanism (Hounsfield, 1973), whereas ultrasound employs sound waves and current machines are manually operated (Wells, 1972). Both types of equipment require supervision by an experienced radiologist if optimal examinations are to be obtained and the images correctly interpreted. Ultrasound scanners have two major disadvantages. Firstly, the quality of the final image is highly dependent upon the skill of the operator and secondly, ultrasound is unable to obtain diagnostic information through bone or gas. The CT images are therefore more reproducible and this equipment can be used to examine the lungs and bone as well. However, against this are the considerably higher capital outlay and running costs of the CT scanner, about ten times those of an ultrasound scanner, and its use of ionizing radiation at a dose which may reach several rads to a given volume in some examinations.

Because the two techniques use different forms of energy, they measure totally different physical characteristics, have different advantages, indications and limitations and are therefore frequently complementary. For the purpose of this paper, we are considering each technique solely on its merits as a diagnostic imaging modality in a group of 50 patients with suspected pancreatic disease.

MATERIALS AND METHODS

Fifty patients have been examined with both a commercial grey scale ultrasound machine (Nuclear Enterprises Diasonograph) and the prototype of the EMI whole body scanner. Both investigations were carried out on the same day in each patient, and the radiologist conducting the examinations had access to a summary of the clinical problems, together with all relevant radiological and laboratory data. The images were read independently and written reports were made. The images on each patient were compared at regular intervals by two observers (H.M. and J.H.). The initial reports issued to the referring clinician were not altered as a result of these comparative analyses.

All patients in this report have been followed up and the final diagnosis was obtained either by laparotomy, post-mortem or by strong biochemical or clinical evidence of disease. Thus the degree of confidence in the final diagnosis necessarily varied according to patient management and the progression of disease. Patients in whom follow-up information was considered to be inadequate have been excluded from this series. The 50 patients included in this analysis are drawn from a total of 63 consecutive patients with suspected pancreatic disease. The diagnostic criterion used in each technique is briefly described.

Ultrasound

The *normal pancreas* is located because of its constant relationship to certain anatomical landmarks, for example, the superior mesenteric artery and the splenic vein. It has a heterogenous echo pattern and the amplitude of these echoes is just above that of normal liver in the majority of patients.

The signs of *acute pancreatitis* include enlargement either diffuse or localized and a reduction in echo amplitudes compared with normal pancreatic tissue. This is believed to be due to oedema within the gland (Burger and Blauenstein, 1974). A pseudocyst is recognized and distinguished from a solid mass by the absence of echoes within it (Leopold, 1975). In *chronic pancreatitis* the contour of the pancreas is irregular and there may be areas of localized enlargement. The amplitude of the echoes throughout the whole gland is higher than normal. Calcification is recognized as areas of extremely high echo intensity. Dilation of the pancreatic duct may be seen occasionally as an echo-free structure following the line of the long axis of the gland.

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Carcinomas produce a localized enlargement of the gland, the outline of which is frequently lobulated. In our experience one characteristic feature of a neoplasm is the high heterogenicity of the echo pattern compared with the normal gland. This also serves to differentiate a carcinoma from enlargement due to acute pancreatitis.

Computerized tomography

The *normal pancreas* appears as a homogenous structure in front of the inferior vena cava and aorta. It has a smooth or finely lobulated outline and is surrounded by a layer of fat. This perivisceral fat plane is helpful in distinguishing pancreatic tissue from adjacent bowel which has a similar absorption value (Haaga *et al.* 1976).

The CT scan in *acute pancreatitis* shows localized or diffuse enlargement of the pancreas and that the absorption values are not appreciably different. It is therefore not possible to distinguish a neoplasm from acute pancreatitis on the basis of the CT scan alone (Haaga *et al*, 1976). Pseudocysts are recognized because they contain fluid which has a low attenuation value (Sagel *et al*, 1976).

The signs of *chronic pancreatitis* include irregularity of the pancreatic contour, localized enlargement and calcification. Less common findings are dilation of the pancreatic duct, fat replacement in the pancreas and inflammatory reaction extending into the tissues surrounding the pancreatic gland, (Kreel, 1976). The most important sign of *carcinoma* is enlargement and alteration of the pancreatic contour. Loss of fat planes surrounding the pancreas has also been described (Haaga *et al.*, 1976).

RESULTS

The final diagnosis established by follow-up in these 50 patients are shown in Table I and the diagnostic accuracy of ultrasound and CT are shown in Table II.

Both techniques successfully visualized the pancreas in all normal patients (Fig. 1) and both diagnosed approximately 80% correctly (Table II). There were two false positives with ultrasound in this group. One scan was interpreted as showing acute pancreatitis as the echo amplitudes were lower than normal. The other false positive examination

TABLE I

TOTAL NUMBER OF PATIENTS—50

Final diagnosis	Number of patients
Normal	14
Acute pancreatitis	8
Chronic pancreatitis	16
Carcinoma	9
Endocrine tumours	2
Lymphoma	1

TABLE II

	Ultrasound						C.A.T.					
	Normal	Pancreatitis Acute	Pancreatitis Chronic	Carcinoma	Endocrine	Lymphoma	Normal	Pancreatitis Acute	Pancreatitis Chronic	Carcinoma	Endocrine	Lymphoma
Correct diagnosis	12	6	8	5		1	11	7	14	9		1
False positive	2	1					3	1				
False negative			1	2	2				2		2	
Technical failure		1	7	2								
Totals	14	8	16	9	2	1	14	8	16	9	2	1

Normal (14 patients).

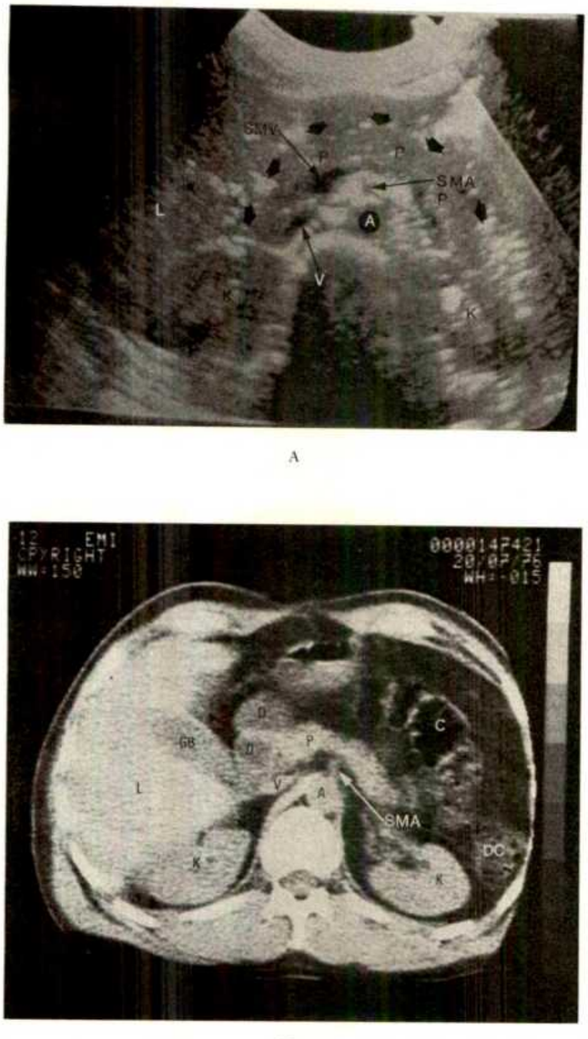


FIG. 1.

(A) Ultrasound scan of normal pancreas.

(B) CT scan of normal pancreas.

Pancreas P, aorta A, inferior vena cava V, kidneys K, liver L, gall-bladder GB, descending colon DC, duodenum D, colon C, superior mesenteric artery SMA, superior mesenteric vein SMV

was reported as chronic pancreatitis since the echo amplitudes were high and the pancreas had an irregular outline.

The three false positive CT examinations were due to difficulty in distinguishing bowel from pancreatic tissue, particularly in the region of the tail. This led to an erroneous diagnosis of pancreatic carcinoma in two patients and chronic pancreatitis in the third. All normal patients were diagnosed correctly by one or other technique.

Acute Pancreatitis (eight patients)

Ultrasound successfully diagnosed acute pancreatitis in six of the eight patients. One examination was a technical failure due to the presence of bowel gas. The one incorrect report was a false positive diagnosis of carcinoma (vid. infra). Pseudocysts were present in three patients and diagnosed correctly by ultrasound in all of these.

The CT scans were interpreted correctly in seven of the eight patients with acute pancreatitis and again all pseudocysts were clearly demonstrated. One false positive diagnosis of carcinoma was made with CT. Findings had also been incorrectly interpreted as a carcinoma with ultrasound as indicated above. This was a young man who had obstructive jaundice and ultrasound and CT showed a 5 cm mass in the head of the pancreas, which was interpreted as a probable carcinoma (Fig. 2). Four weeks later, his jaundice had cleared spontaneously and repeat ultrasound and CT examinations were normal. We therefore conclude that this patient had a localized area of pancreatic enlargement secondary to calculus obstruction of the common duct. In retrospect the echo amplitudes within the mass on the ultrasound image were rather lower than we have seen in most carcinomata (Fig. 4A) and are similar to those seen in acute pancreatitis (Fig. 3A). The CT attenuation numbers within the mass were not helpful in differentiating this lesion from a carcinoma.

Chronic Pancreatitis (16 patients)

Chronic pancreatitis was correctly diagnosed in eight (50%) using ultrasound. There were seven unsuccessful examinations and one false negative examination in whom the pancreas appeared normal. In this patient, the CT scan correctly suggested enlargement consistent with pancreatitis.

CT successfully demonstrated lesions in 14 of the 16 patients with chronic pancreatitis. There were two false negative examinations, one had an enlarged pancreas correctly diagnosed on ultrasound and reported as normal on the CT scan. The other patient had histological evidence of pancreatitis at laparotomy but the CT scan appeared normal. Ultrasound failed to visualize the pancreas in this patient.

Tumours (12 patients): *Carcinoma* (nine patients)

Ultrasound succeeded in diagnosing only five of the nine carcinomata (Fig. 4A). Gas prevented visualization in two patients and in one the mass was detected, but misinterpreted as a pseudocyst, and in another the small tumour in the body successfully

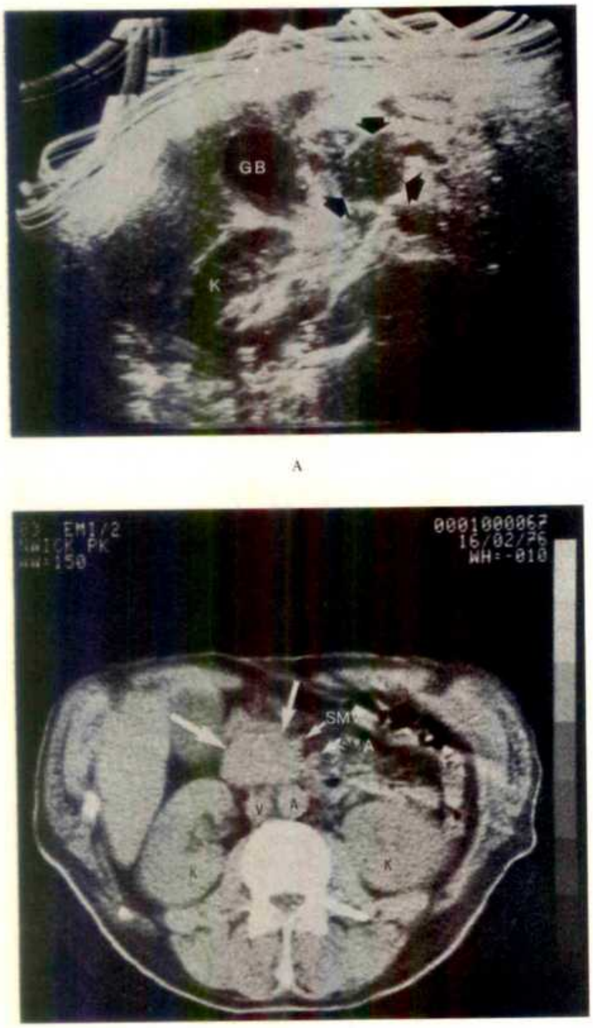


Fig. 2.

(A) Ultrasound scan showing mass in head of pancreas (arrowed).

(B) CT scan of the same patient.

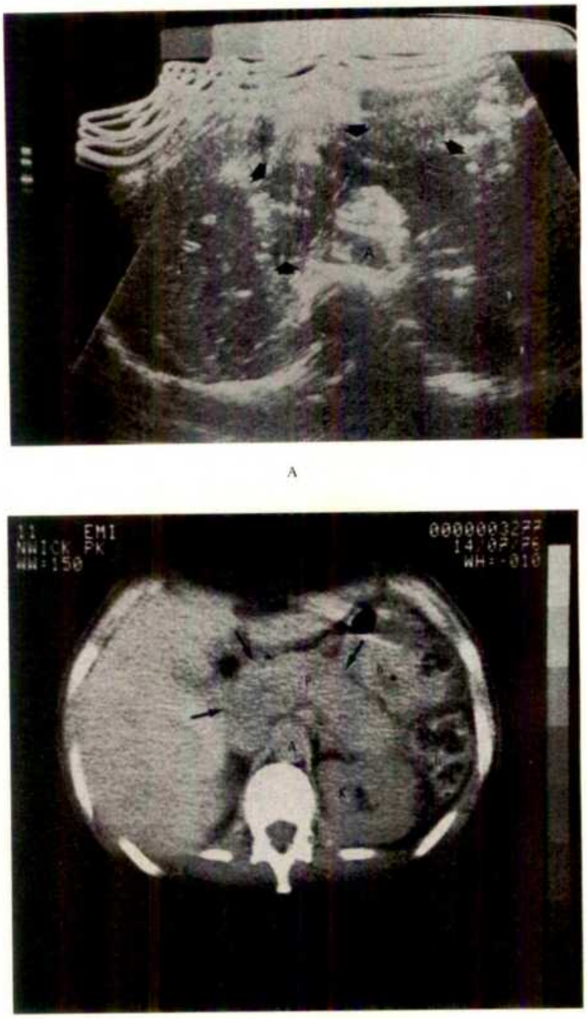


Fig. 3.

(A) Ultrasound scan.

(B) CT scan showing diffuse enlargement of the pancreas (arrowed) in pancreatitis.

detected by CT (Fig. 4B) was missed on a technically poor ultrasound examination. CT correctly diagnosed all nine carcinomata in this series, the smallest lesion detected was in the body, the diagnosis being based upon the extra-pancreatic extension of the tumour measuring approximately 2 cm by 3 cm in diameter (Fig. 4B).

Endocrine Tumours (two patients)

Two patients were referred with clinical and biochemical evidence of a gastrinoma. In neither patient was a lesion detected by either technique.

Lymphoma (one patient)

One patient in this study has been finally diagnosed as having a lymphoma. He is a young man first seen early in 1976 with obstructive jaundice and shown at laparotomy to have a tumour in the region of the common bile duct or head of the pancreas. A biopsy was said to be consistent with carcinoma and no definitive surgical procedure was performed. His jaundice nevertheless regressed, his weight increased and he was referred to Northwick Park for further evaluations. Ultrasound scan revealed a lobulated mass in the porta hepatis, apparently separate from

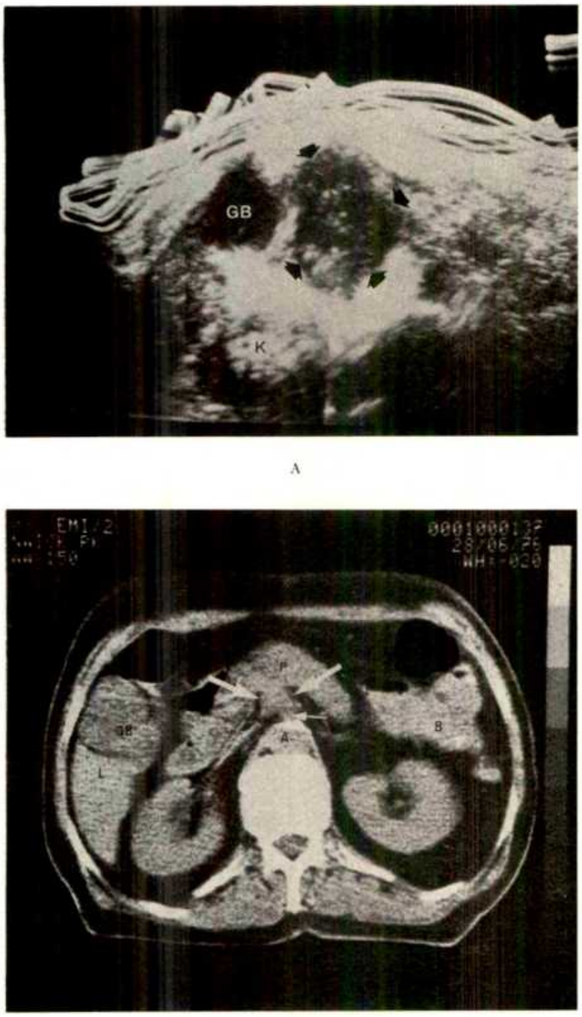


FIG. 4.

(A) Ultrasound scan of carcinoma of head of pancreas (arrowed).

(B) CT scan showing a small carcinoma projecting posteriorly from the body of the pancreas (arrowed) SMA small arrow.

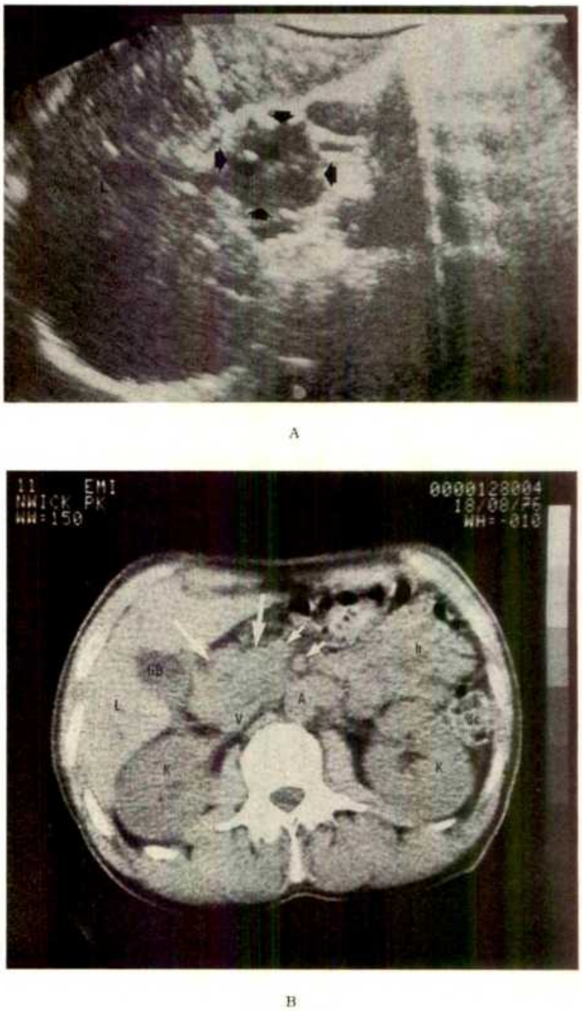


FIG. 5.

(A) Ultrasound scan.

(B) CT scan showing a mass adjacent to the head of the pancreas (arrowed) in a patient with lymphoma. Mesenteric vessels—small arrows

the pancreas (Fig 5A). The echo amplitudes within the mass were very low and more suggestive of a lymphoma than of carcinoma. CT also showed the mass clearly (Fig. 5B) but it was not possible to exclude a pancreatic origin. CT scan also suggested the presence of enlarged para-aortic lymph nodes, a lymphogram was advised to exclude a lymphoma and showed an enlarged lymph node at the level of L2 with a lymphoma pattern of cross striation. Review of histology confirmed the diagnosis of lymphoma. It is therefore concluded that the mass in the porta hepatis and surrounding the head of the pancreas was indeed a mass of lymph nodes.

DISCUSSION

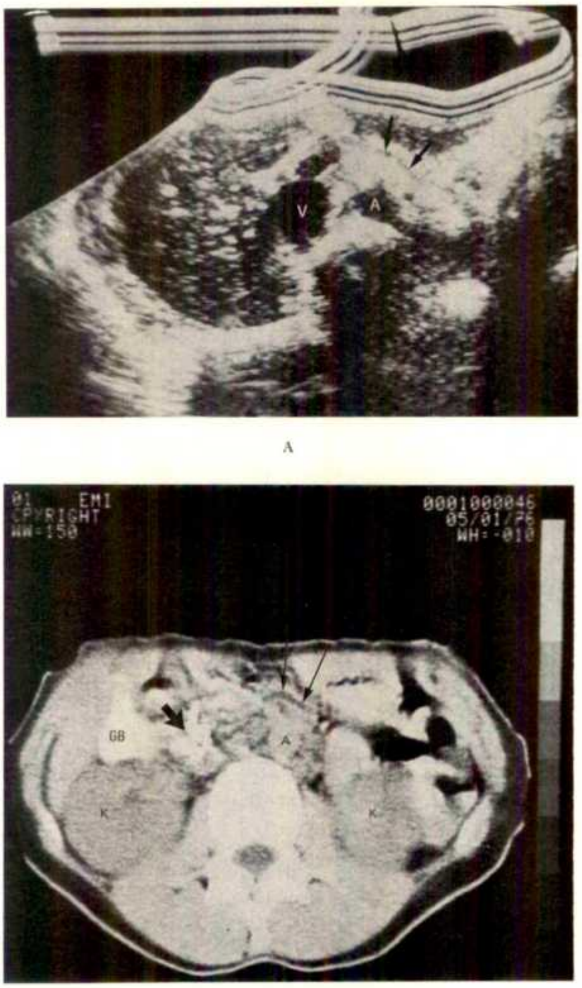
Ultrasound was successful in visualizing the pancreas in all normal patients which represents a significant improvement over previous attempts without grey scale display (Filly and Freimanis, 1970; Engelhart and Blauenstein, 1970; Burger and Blauenstein, 1974) and compares favourably with the findings of Leopold (1975), Haber *et al.* (1976)

and Doust and Pearce (1976). Ultrasonic scanning correctly diagnosed 12 of the 14 patients with a normal pancreas, but only eight of the 16 patients with chronic pancreatitis, and five of the nine with carcinomata. In this small study the results suggest that a normal pancreatic ultrasound correlated well with the absence of pancreatic disease. In a normal clinical environment, patients with failed ultrasound examinations would have had repeat tests a day later, which would be expected to achieve further success in approximately 50% (Haber *et al.*, 1976). This was not possible in our study as the majority of patients came from other hospitals especially for these examinations and repeat journeys were not thought justifiable. It is probable that the success rate for visualization of the pancreas with ultrasound would reach at least 85% by a combination of patient preparation to reduce bowel gas and the availability of repeat examinations (Haber *et al.*, 1976).

In our experience, the normal pancreas is clearly shown by computerized tomography in the majority of patients (Husband and Kreel, 1977; Kreel, 1976). In this study, the normal pancreas was clearly seen in all patients. These findings compare favourably with other published work (Sheedy *et al.*, 1976), describing their results as encouraging but not quoting figures (Stanley *et al.*, 1976), seeing five of eight confirmed normals (Haaga *et al.*, 1976) being successful in 61 of 71 patients while Wiggans *et al.* (1976) failed to identify 67% of pancreatic masses less than 10 cm diameter.

The perivisceral fat plane surrounding the pancreas may be extremely thin or even absent in patients with severe chronic pancreatitis, or in patients with large tumours invading the extrapancreatic tissue. In such instances, the pancreas may be difficult or impossible to outline. Fortunately, ultrasound is particularly successful in this group of patients but fails more often in obese patients in whom CT is very successful. Even in patients with a well-defined layer of fat surrounding the pancreas, problems not uncommonly arise in distinguishing the pancreas from surrounding structures. Our three false positive examinations with CT illustrate this difficulty and we are now attempting to avoid such errors in the future by giving positive contrast medium orally to act as a marker in the duodenum and jejunum (2.5 ml sodium/meglumine diatrizoate (Gastrografin) diluted in 500 ml water is given ten minutes before the scan).

The radiological signs of acute and chronic pancreatitis are well shown by computerized tomography (Kreel, 1976; Husband and Kreel, 1977), but distinction between a localized inflammatory mass and a neoplasm is still not possible (Haaga *et al.*, 1976). Although there is little difficulty in making the diagnosis of severe, acute or chronic pancreatitis by clinical and biochemical means, additional signs of disease may be shown by ultrasound and CT, for example pseudocyst, abscess or dilated pancreatic duct (Fig. 6). Important clinical questions may therefore be answered, for example, is there a pseudocyst and is the pancreatic duct obstructed or dilated? This information may significantly alter patient management as surgery is frequently indicated in the presence of such complications. Both



A

B

FIG. 6.

(A) Ultrasound scan.

(B) CT scan showing dilation of the pancreatic duct (small arrows) in a patient with chronic pancreatitis. The CT scan also shows the presence of calcifications (large arrow).

ultrasound and computerized tomography are clearly of considerable value in this clinical situation.

Obstructive jaundice was confirmed by ultrasound visualization of dilated bile ducts within the liver in all jaundiced patients in this series (five patients). Liver examination is an important prerequisite in such patients, as we have occasionally seen medical causes of jaundice incorrectly diagnosed as surgical. The failure of ultrasound to diagnose four of the carcinomata is obviously disappointing. In one of the false negative examinations, the mass was incorrectly interpreted as a cyst; this examination would not now have been accepted as adequate. Repeat examination of this patient and the other two in whom the pancreas was not visualized might have led to a greater degree of success. The demonstration of all carcinomata by CT is worthy of note and compares favourably with the experiences of Wiggans *et al.* (1976), especially as relatively small lesions were detected. Improvement in equipment, interpretation and possible use of contrast media may well reduce the size of detectable lesions still further. It is important to emphasize that we are unable to recognize endocrine tumours either by ultrasound or CT. These tumours are small and since they are intrapancreatic there is no change in the contour of the gland. Change in contour is the most valuable sign in the diagnosis of pancreatic tumours and we are therefore unable to demonstrate extremely small lesions at the present time. The use of contrast to enhance density difference has also been unrewarding.

It is hoped that the future developments will be accompanied by a significant improvement in the methods of treating carcinoma of the pancreas, a currently hopeless disease (Baylor and Berg, 1973).

This preliminary study has led us to believe that the diagnostic potential of both ultrasound and computerized tomography is somewhat similar in this group of patients. However, the current operator dependence of ultrasound imaging and its inability to examine through gas filled bowel significantly reduces the realization of this potential. Although more expensive CT is therefore, at the present time, the more reliable technique for demonstrating pancreatic lesions, the ready availability and relative cheapness of ultrasound are important features to be considered in attempting to assess the roles of these two techniques.

Some of the patients included in this analysis were examined early in our experience when the probability of error was high. It is hoped that our ability to make the correct diagnosis will improve as further knowledge is gained. We anticipate that this will be due largely to a reduction in the number of false positive examinations of computerized tomography and the technical failures of ultrasound.

The main conclusion drawn from this study of 50 patients is that where both techniques are available ultrasound may be used as a screening procedure from which about 15% of patients may be referred for other diagnostic procedures including computerized tomography. It must be remembered that both techniques are in their infancy and that very significant advances can be expected, with improvements in spatial and density resolution of the CT scanner and in the development of the automatic ultrasound scanner.

Acknowledgments

Grateful acknowledgment is made to the Department of Health and Social Security whose far-sighted and generous help has assisted greatly in the development of this project. The assistance and considerable help from Mr. John Twydle, who has been managing the machine, is also gratefully acknowledged. We are also grateful to Dr. Peter Cotton, who referred many of the patients to us for investigation.

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Book review

Trends in Childhood Cancer. Edited by Milton H. Donaldson and H. Gunter Seydel, pp. vii+144, 1976 (John Wiley & Sons, New York), £12·40.

This small volume consists of the papers presented at the fifth annual symposium on childhood cancer at the Children's Hospital in Philadelphia.

The papers by this group of experts in paediatric oncology covered many aspects of this subject, including a well argued case for special centres for children with tumours, to ensure that all disciplines necessary for management are available both for diagnosis and treatment, a case that cannot be stressed too often. Mention was also made of the need to study late effects and how these might be either managed when they occur or minimized in future management, a study made more desirable by the ever increasing numbers of children being successfully treated for cancer in childhood.

Two papers summarize very well the present state of our knowledge on the various possible causes and the relationship between cancer and immune competence of the host.

The management of the lymphomas and leukaemias is dealt with in several papers, which together cover the overall management of children with these conditions.

Three solid tumours, Ewing's, neuroblastoma and retinoblastoma are well documented with an up to date appraisal of our understanding and treatment of these tumours.

The two contributions on rhabomyosarcoma and Wilms' tumour on the other hand were disappointing.

In summary there was a lot of material in this symposium, but much of it is available elsewhere and this slim volume is certainly rather expensive.

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A lymphographic study of chyluria

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ABSTRACT

Ninety patients with chyluria were studied by bilateral pedal lymphography. The retroperitoneal lymphatic vessels were dilated, tortuous and increased in number in 61% of cases while the appearance of the lymph nodes was abnormal in 67% of cases. Renal lymphatic reflux, either bilateral or unilateral, was seen in 93% of patients. A correlation ($P > 0.007$) was observed between the site of origin of the cisterna chyli and side of unilateral renal lymphatic reflux. There was no evidence of thoracic duct obstruction although the thoracic duct was more than 3 mm in calibre in seven cases. Lymphography was also performed on 22 patients who had undergone stripping of the lymphatics along the renal pedicle to determine if surgical disconnection was complete. The pathogenesis of chyluria is briefly discussed.

Chyluria is characterized by the presence of fat globules in the urine and is sometimes accompanied by haematuria. If blood clots or chylous clots are passed, the patient may present with ureteric colic. When chyluria is severe, wasting, hypoproteinaemia, lymphopenia and anaemia may be present. Chyluria has an intermittent pattern, especially during the early course of the disease. It is relatively common in Asia, Africa and Latin America although extremely rare in Great Britain. Various aetiological factors have been cited to explain the pathogenesis of chyluria. In patients residing in the tropics, chyluria has been attributed usually to filarial infection. Trauma, malignancy and congenital abnormality of the lymphatic vessels and thoracic duct have been implicated in the aetiology of non-parasitic chyluria. Patients with mild chyluria can usually be managed conservatively by dietary restriction of fat. Surgery is only contemplated if the chyluria does not respond to dietary measures and is of such severity that marked wasting continues or if ureteric colic or clot retention caused by the passage of chylous or blood clots occurs. Skeletonization of the renal pedicles and upper ureter via the retroperitoneal route on the side with unilateral lymphatic reflux is the procedure of choice. Chyluria invariably stops if lymphatic disconnection is complete. When bilateral renal lymphatic reflux is present, surgery is normally carried out only on the side with the more severe reflux. The chyluria should either cease completely or at least become less severe. Lymphatic disconnection in the contralateral kidney is usually unnecessary (Koo and Langenberg, 1969; Yu *et al.*, 1977). Apart from the papers by Craig and Woodroffe (1969) and by Ko *et al.* (1975), there is very little in the British radiological literature on the subject.

MATERIAL AND METHOD

Ninety patients with chyluria were studied by bilateral pedal lymphography. Fifty of these patients were male and 40 were female. The ages ranged from 23 to 78 years. The standard technique of identification and cannulation of the lymphatic vessels at the dorsum of the feet was used (Kinmonth *et al.*, 1955). 8–10 ml of Lipiodol ultra-fluid was injected into each leg with the aid of a "gravity" pump at a rate of 6 ml of contrast medium per hour. Films were taken during the filling phase of the lymphographic examination with the patient supine and these were analysed with reference to the appearance of the lymphatic vessels and thoracic duct, the presence of Lipiodol ultra-fluid in the renal lymphatics, in the calyceal systems and in the bladder. The 24-hour films were analysed with reference to the appearance of the opacified inguinal, pelvic and para-aortic lymph nodes. Eighty-eight patients had undergone lymphographic examination during the initial work-up to confirm the diagnosis and to assess the site and severity of the lymphatic abnormality. Lymphography was repeated on 20 of these patients after surgery to determine whether the disconnection was complete. Post-surgery lymphography was also carried out on two patients who did not undergo pre-operative lymphographic examination: chyluria continued in one patient after surgery while chyluria recurred in the other patient three years after operation.

RESULTS

Lymphatic vessels (Table I)

The lymphatics in the thigh were normal in all our patients with the exception of one in which several of the lymphatics ended abruptly (Fig. 1). The lymphatics in the pelvic and para-aortic regions were normal in 34 patients. These lymphatics were dilated, tortuous and more numerous than normal in 54 patients. In all these patients, the abnormality

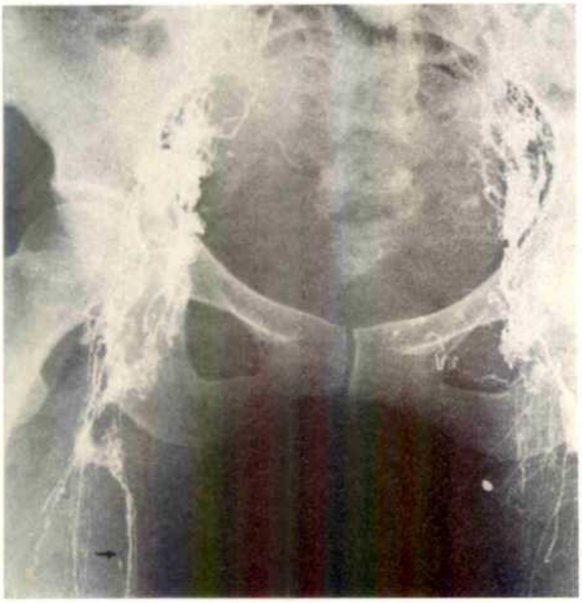


Fig. 1.
Abrupt termination of a lymphatic vessel in the right thigh (arrowed).

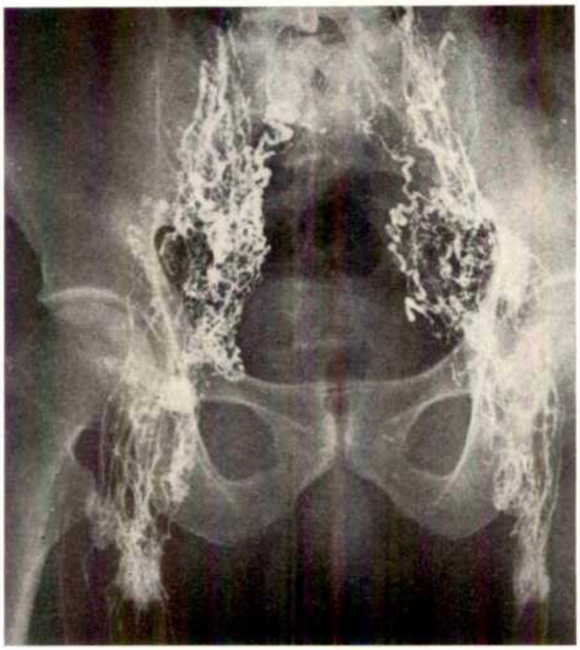


Fig. 2.
Numerous dilated and tortuous lymphatic vessels above the inguinal lymph nodes.

TABLE I
Appearance of pelvic and para-aortic lymphatic vessels

Normal	34
Dilated, tortuous, increased in number	54
Total	88

TABLE II
Appearance of thoracic duct

Normal	73
> 3 mm in calibre	7
Not visualized	8

commenced abruptly above the inguinal lymph nodes (Fig. 2). A large lymphadenovarix, which consists of a tangled mass of varicosed lymphatics and nodes, was present in the pelvis of the patient with concomitant lymphatic abnormality in the thigh (Fig. 3A and 3B). Aneurysmal dilatation of the pelvic lymphatics was seen in another patient (Fig. 4). Lymphocysts were seen in three patients: two in the para-aortic region and one in the mediastinum (Fig. 5). A patient demonstrated reflux of the contrast from the left inguinal region down to the scrotel lymphatics (Fig. 6).

Thoracic duct (Table II)

In eight patients, the thoracic duct was insufficiently opacified to determine its patency or calibre. In the remaining 80 patients, there was no evidence of obstruction of the thoracic duct along its entire length. The calibre of the thoracic duct was less than 3 mm in 73 patients but more than 3 mm in seven patients. The cisterna chyli was clearly defined in 72 patients: it was in the mid-line in 37 patients, to the right of the mid-line in 12 patients and to the left of the mid-line in 15 patients. In seven cases, the cisterna chyli had a bifid origin with one tributory arising from the mid-line and the other from the left of the mid-line. In one case, the cisterna chyli also had a bifid origin, but with tributaries arising from the right and the left of the mid-line.

Opacification of renal lymphatics and calyceal systems (Table III)

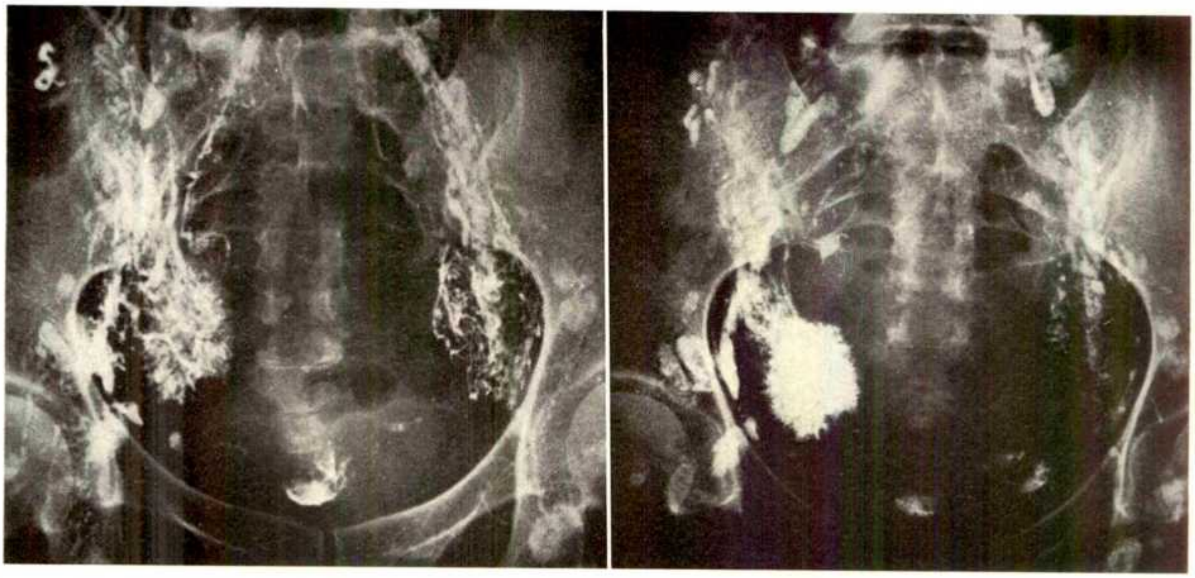


FIG. 3.
A large lymphadenovarix in the right side of the pelvis during different phases of filling with contrast. Note that contrast is also present in the bladder.

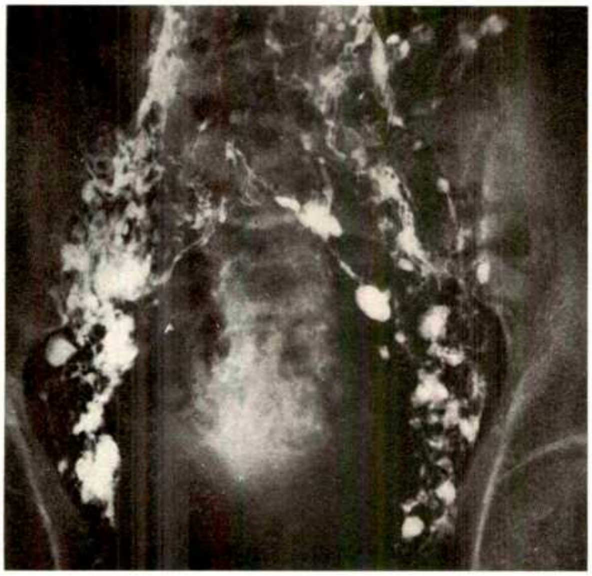


FIG. 4.
Tortuous pelvic lymphatics with "aneurysmal" dilatation.

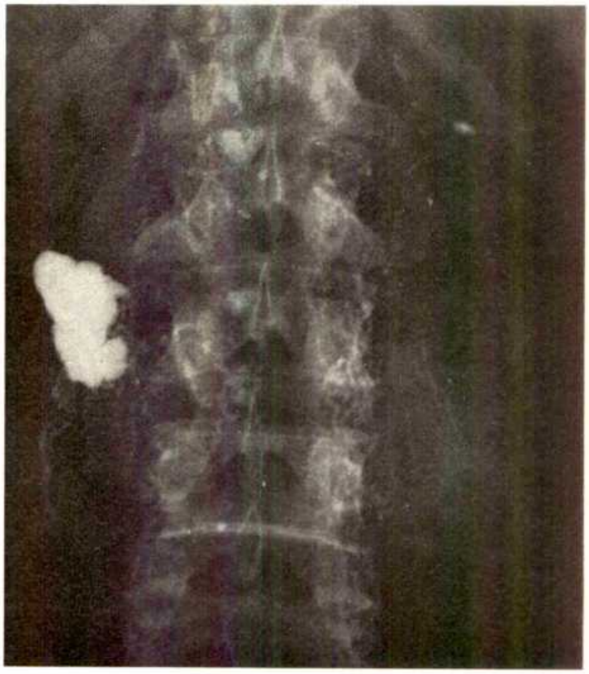


FIG. 5.
A lymphocyst in the right para-aortic region.

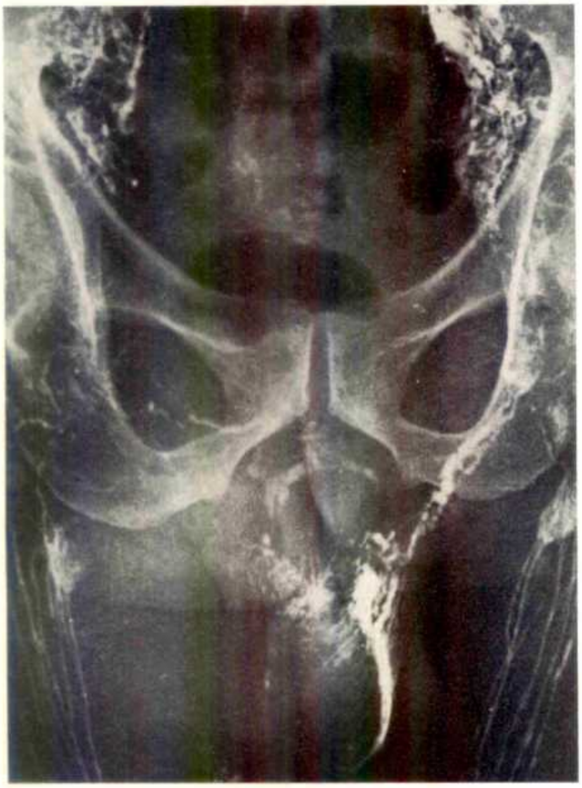


Fig. 6.
Reflux of contrast from the left inguinal region to the scrotal lymphatics.

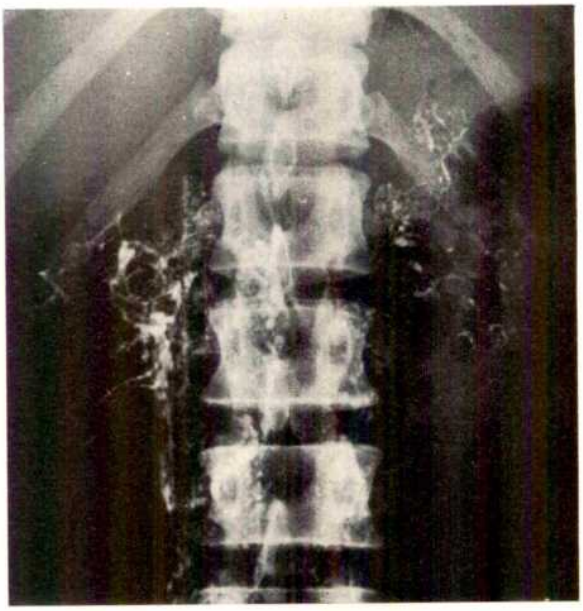


Fig. 7.
Opacification of the renal lymphatics on both sides. The lower end of the thoracic duct is mid-line in position.

TABLE III
Opacification of renal lymphatics and calyceal systems

Right renal lymphatics only	16
Left renal lymphatics only	32
Renal lymphatics on both sides	34
No opacification of renal lymphatics	6
Right calyceal system only	10
Left calyceal system only	20
Both calyceal systems	2
Bladder	17

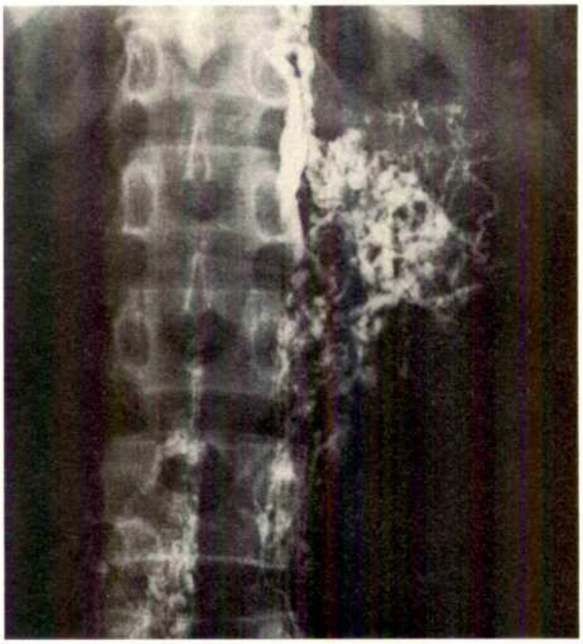


Fig. 8.
Opacification of the left renal lymphatics. The lower end of the thoracic duct is to the left of the mid-line.

There was reflux of the contrast medium into the renal lymphatics on both sides in 34 cases (Fig. 7), to the lymphatics of the right kidney only in 16 cases, and to the lymphatics in the left kidney only in 32 cases (Fig. 8). In six patients, reflux could not be

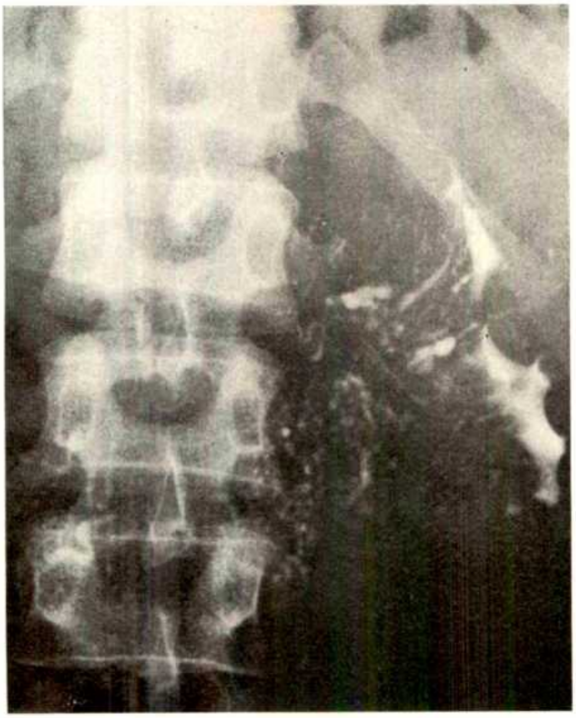


Fig. 9.
Opacification of the left renal lymphatics and calyceal system.

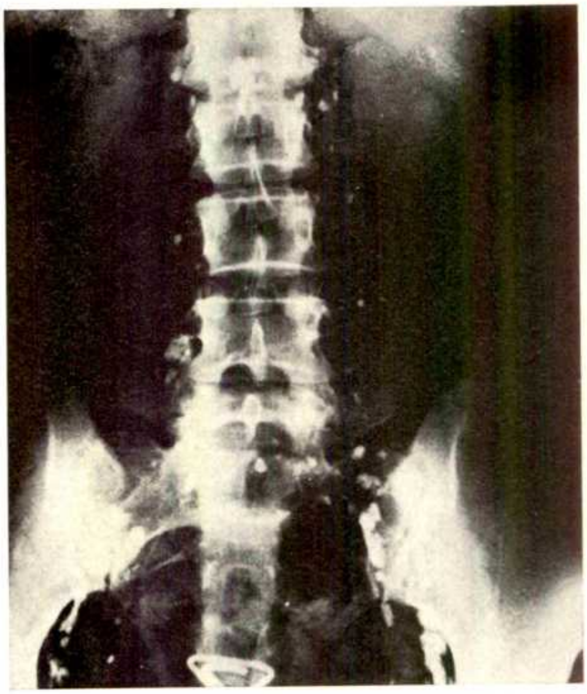
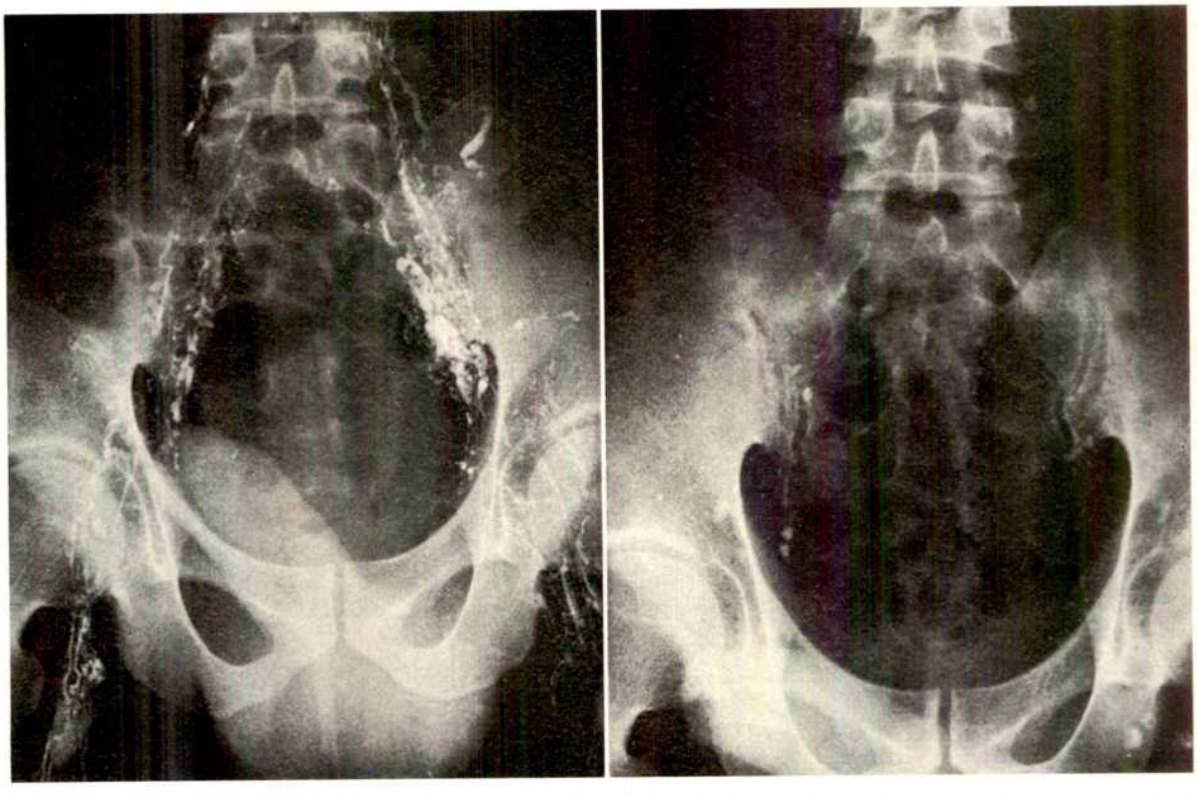


Fig. 10.
The retroperitoneal lymph nodes are small and sparsely distributed.



A Fig. 11. B
(A) Dilated and tortuous lymphatic vessels in the pelvic and lower para-aortic regions during the filling phase. (B) There is almost complete absence of opacification of the lymph nodes in the same regions in the 24-hour film.

demonstrated. The contrast medium was seen in the calyceal system on both sides in two cases, in the right calyceal system only in ten cases, in the left calyceal system only in 20 cases (Fig. 9), and in the bladder in 17 cases. (Fig. 3A and 3B). In none of these cases was there direct reflux of the contrast medium from the pelvic lymphatics to those in the bladder and thence to the vesical lumen.

Appearance of lymph nodes (Table IV)

The lymph nodes were normal in 32 cases. They were smaller and fewer than normal in 17 cases (Fig. 10), normal in size but fewer in number in 21 cases, and normal in number but small in size in six cases. In some there were virtually no opacified nodes in the retroperitoneal regions (Fig. 11A and 11B). In 15 cases, the lymph nodes were enlarged and had a coarse reticular pattern reminiscent of lymphoma (Fig. 12). In three patients, small and enlarged nodes co-existed in different regions.

Post-operative lymphogram (Table V)

Post-operative lymphography was performed on 22 patients, usually six weeks after operation. In 19 patients who had undergone unilateral stripping, renal lymphatic reflux was no longer present on the repeated lymphograms in all but one of these cases on the side in which surgery had been performed (Fig. 13A and 13B; Fig. 14A and 14B). Three patients were referred to us from other hospitals because the chyluria either recurred or continued after surgery. Bilateral stripping had been performed simultaneously in all these cases: one by the transperitoneal route, and two by the retroperitoneal route. The post-operative lymphogram showed persistent bilateral renal reflux in one patient and left renal reflux in the other two.

TABLE IV

APPEARANCE OF PELVIC AND PARA-AORTIC NODES

Normal	32
Sparse and/or small	44
Enlarged with abnormal pattern	15

TABLE V

POST-OPERATIVE LYMPHOGRAM RESULTS

Number of patients with post-operative lymphograms	22
Number of patients undergoing unilateral stripping of renal lymphatics	19
Number of patients showing persistent opacification of renal lymphatics on the side of surgery	1
Number of patients undergoing simultaneous bilateral stripping of renal lymphatics	3
Number of patients showing persistent opacification of renal lymphatics	3 (2 on left and 1 on both sides)

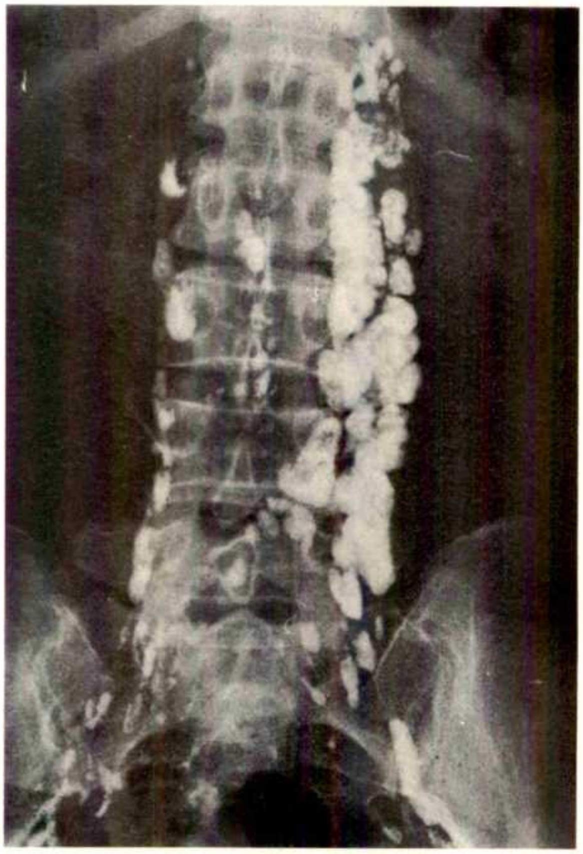


FIG. 12.

Enlarged nodes with coarse-reticular pattern in the left para-aortic region.

DISCUSSION

Although complete opacification of the entire thoracic duct has been considered to be evidence of disturbed lymphatic dynamics (Sen, 1974), we have frequently encountered complete opacification of the whole or almost the entirety of the thoracic duct during lymphography in patients in whom there was no

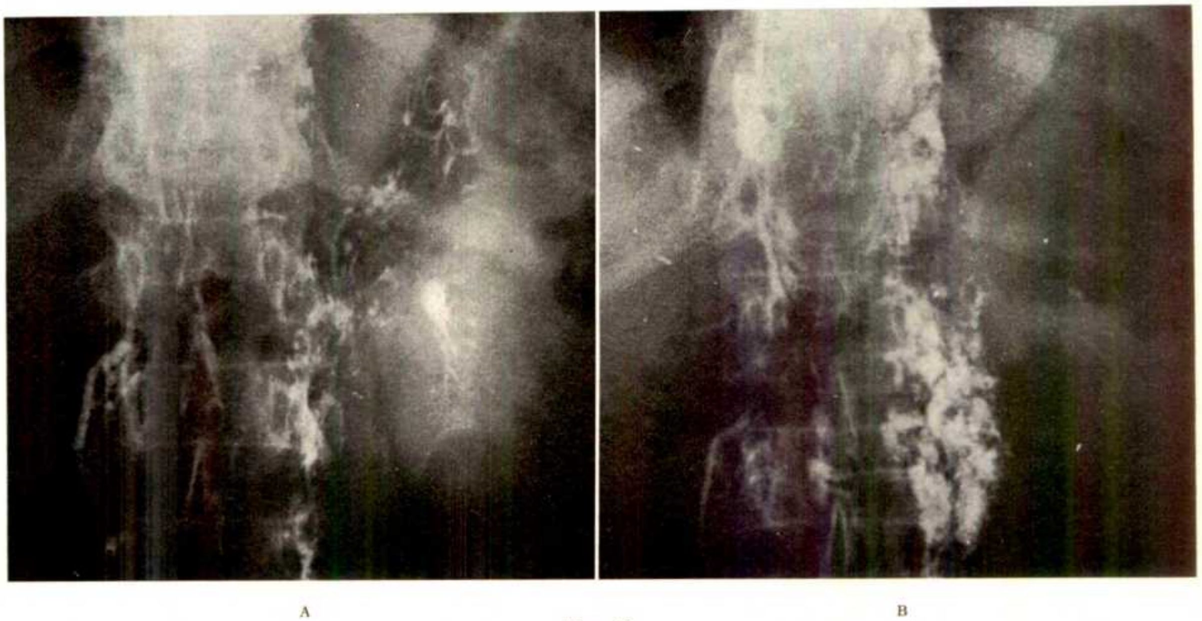


FIG. 13.
(A) Unilateral reflux of contrast to the left renal lymphatics. There is also opacification of part of the calyceal system. (B) Absence of reflux of contrast to the left renal lymphatics in the repeated lymphogram after surgery on this side. Note that the lower end of the thoracic duct is to the right of the mid-line.

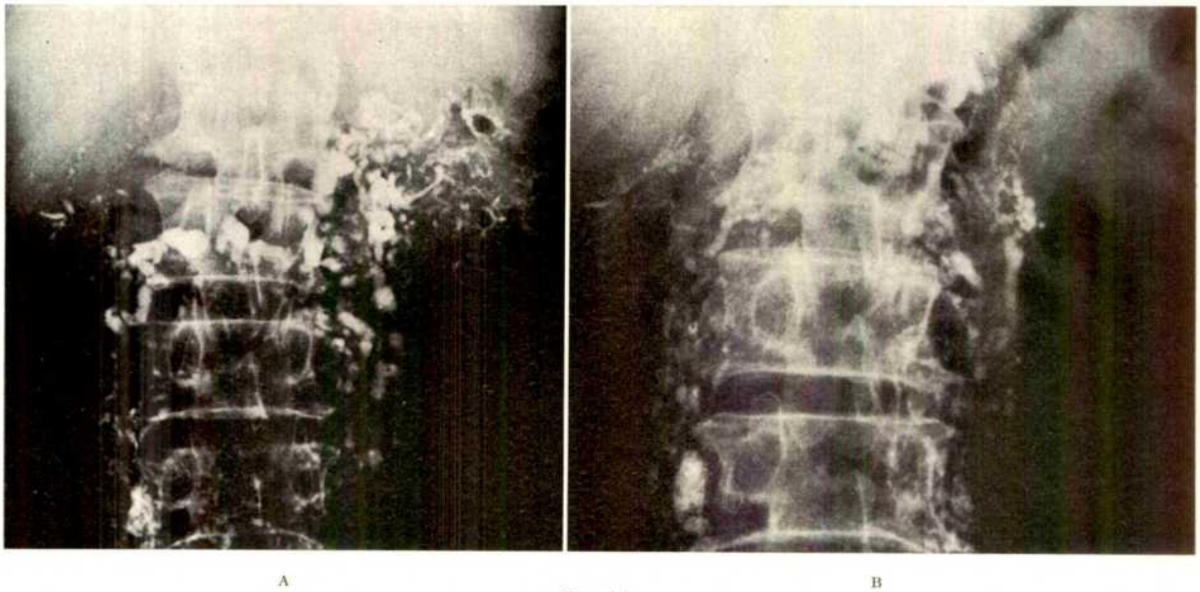


FIG. 14.
(A) Reflux of the contrast medium to the renal lymphatics on both sides but more severe on the left. (B) Absence of reflux of contrast to the left renal lymphatics in the repeated lymphogram after surgery on the left side. No change in the amount of reflux to the right renal lymphatics. The lower end of the thoracic duct is left-sided.

reason to suspect any abnormality of the thoracic duct. The completeness of filling is probably determined by the technique used during lymphography and is related to the amount and rate of injection of the contrast medium and the timing of the films. Sen (1974) observed that the thoracic duct was dilated and more than 3 mm at its widest in all his patients with chyluria. Akisada and Tani (1968) also observed similar findings in 63.2% of 30 patients studied. However, the calibre of the thoracic duct was less

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than 3 mm in its widest extent in 91% of our patients and is more in keeping with the experience of Koehler *et al.* (1968) who found that the thoracic duct was normal in the majority of cases. Lymphatic obstruction, therefore, cannot be implicated as the cause of chyluria in our patients.

When unilateral renal lymphatic reflux occurs, the left side is involved more often than the right (Koehler *et al.*, 1968) and this has been our observation in the present series. If renal lymphatic reflux is caused directly by lymphatic obstruction, it is surprising that there should be this prediction on the left. In our patients with right-sided unilateral renal reflux, the cisterna chyli was always situated either at the mid-line or to the right of the mid-line. In those with left-sided unilateral renal reflux, the cisterna chyli was situated either at the mid-line or to the left of the mid-line in all but two cases, in which the cisterna chyli was right-sided. This observation suggests that there is a correlation between the site of origin of the cisterna chyli with reference to the mid-line and the side on which unilateral renal lymphatic reflux occur ($P > 0.007$). In the absence of organic obstruction to the thoracic duct, it is tempting to postulate that disturbance in the dynamics of the lymph flow from the renal lymphatics to the cisterna chyli, either on the basis of functional incompetence of the valves or of abnormal peristalsis in the lymphatic vessels and thoracic duct, may be the aetiological factor in the pathogenesis of chyluria. Thus retrograde flow of the lymph is more likely to occur in the renal lymphatics on the side nearer to the lower end of the thoracic duct than the opposite side.

In patients with chyluria, there is often a paucity or even complete absence of retroperitoneal nodes on the lymphogram (Ko *et al.*, 1975; Sen, 1974). This has also been our experience in this series, although we observed that the lymph nodes were also small in size in some of our patients (Table IV). The lymphographic abnormality is conventionally believed to be due to lymphatic obstruction resulting in some of the nodes being by-passed. However, this hypothesis cannot explain the reduction in size in the nodes. Loss of lymphoid tissue or fibrosis associated with filarial infection may be the alternative explanation for the smallness of some of the nodes and the same pathological process may eventually lead to complete non-opacification. It is interesting to observe that in 16% of our patients, the opacified lymph nodes, mostly in the para-aortic region, were enlarged with a coarse reticular pattern reminiscent of lymphoma. Akisada and Tani (1968) mentioned that this appearance was seen in their early cases of filarial infection. Experimental work on cats which were infected with B. pahangi demonstrated that the lymph nodes enlarged as a result of reactive hyperplasia during the initial stage of filarial infection, but became smaller in longstanding infection (Gooneratne, 1974). Thus, if the lymphadenographic abnormalities were indeed caused by filarial infection in our cases, the different appearances encountered could simply represent different stages of the disease.

Only two of our patients gave a history suggestive of filarial infection in the past and repeated nocturnal blood samples failed to demonstrate the presence of microfilariae of Wuchereria bancrofti (Yu *et al.*, 1977). In a separate study (unpublished) we have biopsied the lymph nodes and lymphatic vessels around the hilum of the kidney during surgery in 20 patients with chyluria. None of these nodes or lymphatics showed the presence of dead worms of Wuchereria bancrofti. Intranodal fibrosis was seen in seven cases. All the lymphatics were dilated and tortuous with mildly thickened walls, but the valves were normal. Eosinophilic infiltration, which suggests the presence of a parasitic infestation, was seen in the nodes and lymphatic in only two cases. These findings, therefore cast doubt that simple organic obstruction due to filarial infection, could be responsible for the clinico-radiological features. Disturbance in flow dynamics in the lymphatic vessels and thoracic duct as a result of the production of toxic metabolic products or immune reaction associated with filarial infection could, however, be the mechanism in the pathogenesis of chyluria.

Acknowledgment

We are grateful to Professor G. B Ong for his advice and permission to study patients under his care.

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Unusual arteriovenous communications presenting as cardiac murmurs in infancy. Report of three cases

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ABSTRACT

Three cases are decribed of infants presenting with murmurs in, or adjacent to, the thorax and considered to be cardiac.

Later full investigations established that the murmurs were due to aorto-azygos fistula, vertebral arterio-venous fistula and intercostal angioma, respectively. While such lesions are extremely rare, the possibility of systemic arterio-venous communication should be considered in infants with atypical murmurs.

In recent years we have seen three unusual and puzzling cases presenting with murmurs in, or adjacent to, the thorax in small children. All these cases presented difficult diagnostic problems and at first the lesion was considered to be cardiac in all. This led to full cardiac investigations. Diagnosis in all was eventually made by selective arteriography of the appropriate area.

CASE REPORTS

Case 1

This five-year-old coloured female presented with a murmur which was heard soon after birth. The murmur was best heard posteriorly at about T5. She had one episode of cyanosis and dysnoea at four days followed by recurrent attacks of bronchitis. At the age of two she was investigated for a left to right shunt by cardiac catheterization. The investigation revealed normal right sided pressures, no left to right shunt, and a normal pulmonary circulation. At the age of five years she was re-admitted for investigation of the murmur. A percutaneous trans-femoral catheterization was performed and injections were made into the aortic root and then into the descending aorta. A fistula was demonstrated between the aorta and the hemi-azygos system. The fistula itself was then catheterized for better visualization. No operation was performed. The patient is attending follow-up clinics (Figs. 1 and 2).

Case 2

This ten-year-old Maltese female presented at the age of one year with a continuous murmur to the left side of the

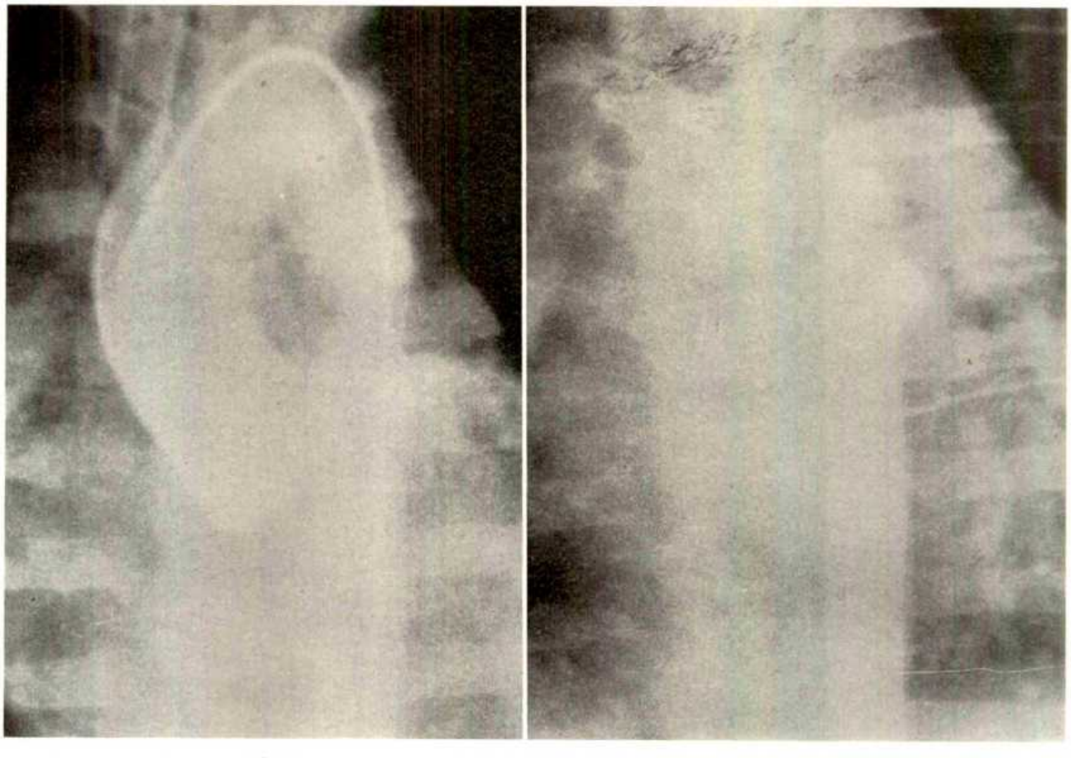
A B

FIG. 1.

Arch aortogram showing unusual vessels superimposed on the descending aorta.

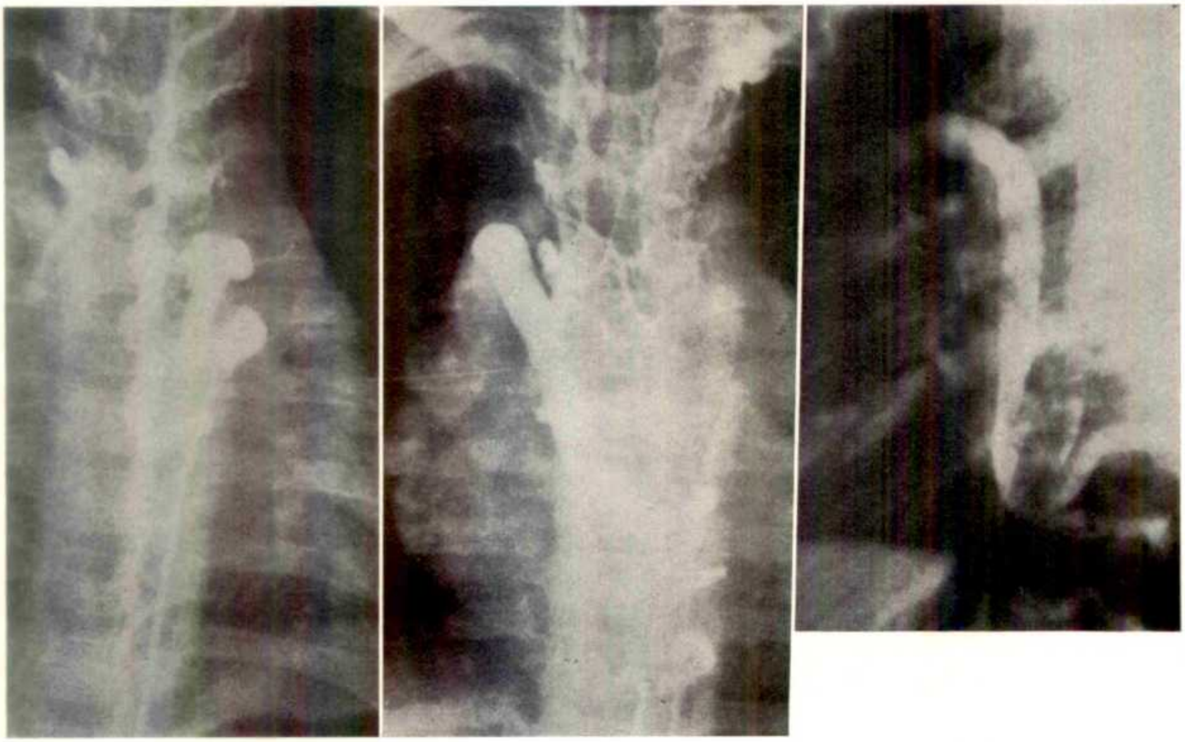

Fig. 2.

Selective injection of large vessel arising from upper descending aorta and feeding directly into the azygos system. (A) Early phase of injection. (B) Late phase of injection showing contrast entering S.V.C. from azygos vein. (C) Lateral film of contrast filled azygos vein.

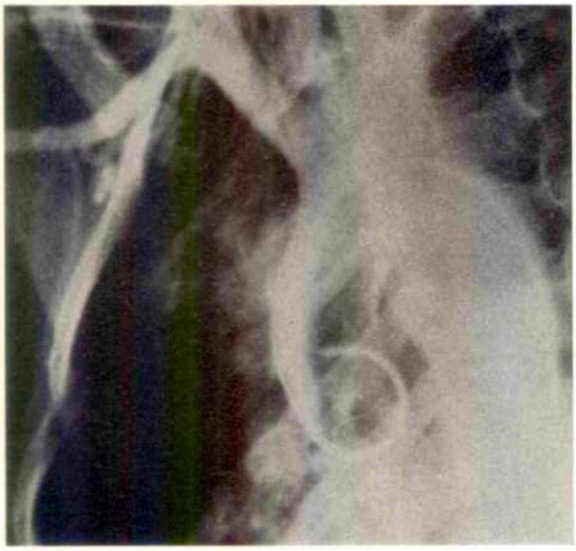

Fig. 3.

Arch aortogram showing abnormal vessels in the right upper thorax.

sternum and recurrent chest infections. A chest X ray at the time showed some left ventricular enlargement and some increase in pulmonary vascularity. A patent ductus was diagnosed and confirmed at right heart catheterization. At the age of two, the ductus, measuring 1 cm × 5 mm was ligated. The aorto-pulmonary root appeared to have a normal configuration with no evidence of a right sided arch or any window. Post operatively a continuous murmur was audible in the right axilla. This was thought to be a pulmonary arterio-venous fistula. The patient was not cyanosed, therefore no treatment was decided upon until she was older. By the age of ten years the murmur had increased in intensity and a chest X ray revealed notching of the second and third ribs. A percutaneous trans-femoral catheterization was performed. An arch aortogram showed evidence of an angioma in the right upper thorax (Fig. 3). A selective right upper intercostal arteriogram was then performed (Fig. 4). This showed the lesion to be supplied by the right supreme intercostal and two upper intercostals. The arterio-venous malformation lay in the second and third intercostal space posteriorly and drainage occurred into the azygos system. At operation the two large feeding arteries and the costocervical trunk were divided. There was gross enlargement of the superior intercostal vein and main azygos trunk and both were divided. Total excision was not performed for fear of injuring the T1 and T2 nerve roots. Post operatively there was no complication and the continuous murmur was no longer audible.

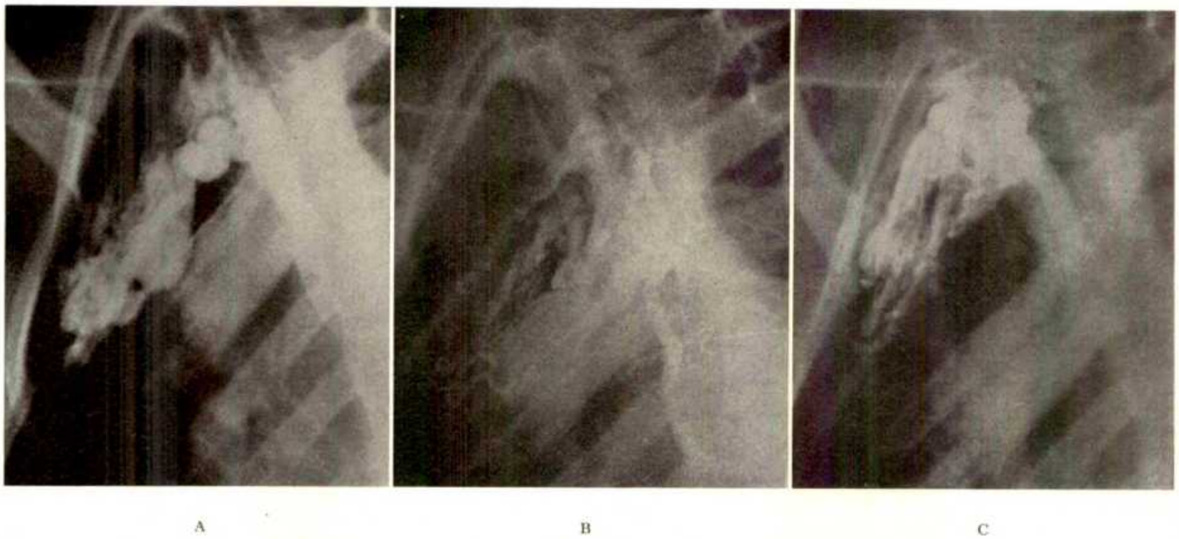

FIG. 4.

(A) Selective injection into dilated right sixth intercostal supplying the angioma. Note the deformity of the second rib and widening of the second interspace. (B) Later phase of same injection showing main drainage vein passing to the azygos vein. (C) Injection of dilated right seventh intercostal which is also supplying the angioma.

Case 3

This female child, aged nine, was admitted to St. Mary's Hospital for the investigation of a loud machinery murmur over the left side of the neck and upper left chest wall. This had first been noticed at the age of one year on examination for bronchitis and had been considered to be cardiac. She was eventually seen by Dr. Edwin Besterman and referred to St. Mary's Hospital at the age of nine. At this time the clinical diagnosis was considered to be a possible carotid jugular fistula. The blood pressure was 100/70 and both femoral pulses were palpable and equal. Arch aortography was performed by trans-femoral catheterization. The arch aortogram showed that there was a right vertebral A.V. fistula. Selective injection of this was performed to elucidate (Figs. 5 and 6). It was considered that surgery at this site would be a hazardous procedure and the patient was treated conservatively.

DISCUSSION

The angiomatous malformation in the upper thorax is perhaps the least remarkable of these cases. Such angiomatous malformations can occur anywhere in the body though it is relatively unusual for them to present in infancy. Perhaps the best known of these lesions to present in small children is an intracranial one. So called aneurysm of the vein of Galen may present with hydrocephalus or signs suggesting an intracranial tumour. Most of these cases are now regarded as associated with angiomatous malformation.

However, angiomas in general tend to present in early adult life unless they are superficial and readily detectable. This may be because the lesions tend to increase in size as adult blood pressure is established.

A.V. fistulae of congenital origin are extremely rare apart from congenital cardiac lesions such as patent ductus. Most arterio-venous fistulae outside the heart are of traumatic origin and because of this are relatively easy to diagnose. Vertebral arterio-venous fistula is well documented as a traumatic lesion though most of the reported cases have been iatrogenic following attempts at direct needle vertebral arteriography. The subject was reviewed by Sutton and Pratt (1971) who reported three personal cases and reviewed the literature. They could find only one report on congenital vertebral arterio-venous fistula (Norman *et al.*, 1950). This case appears to be very similar to the one we report in that a six-month-old child presented with a respiratory infection and developed cardiac failure on the third day after admission at which time a loud continuous bruit and thrill were discovered in the left posterior triangle of the neck. At operation a fistula between the vertebral artery and vein at the level of C2 was dissected out, ligated and removed. Following this the cardiac failure was rapidly brought under control. It would appear therefore that the case now being reported by us is similar since there is no history of direct trauma and we can regard it as a true congenital arterio-venous fistula.

Case 1 of the aorto-azygos fistula appears to be unique and we can find no similar case report in the literature. Again, there is no evidence of trauma and

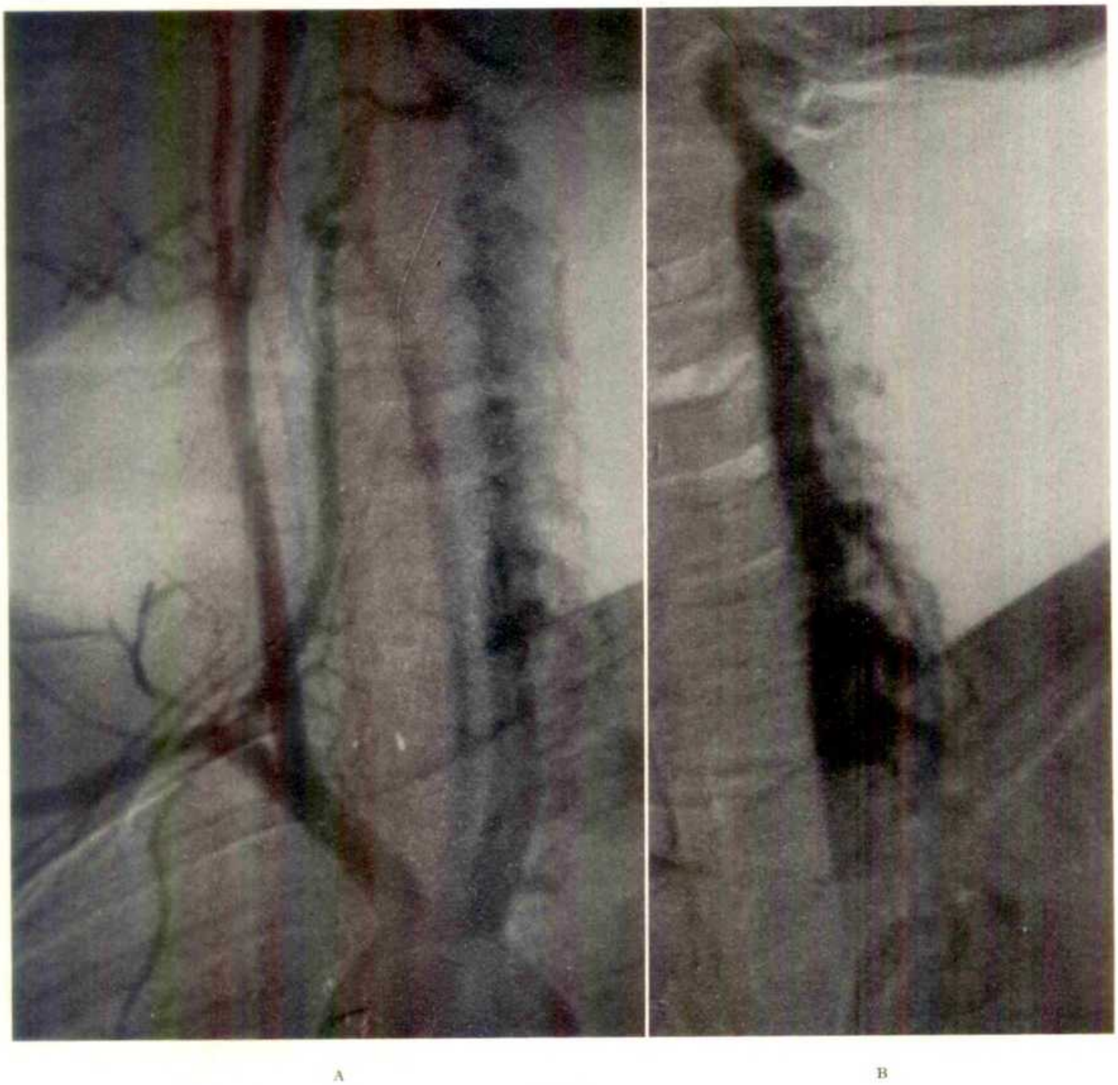

Fig. 5.

(A) Arch aortogram showing dilated vertebral artery with fistula. (B) Selective injection of the vertebral artery showing the fistula more clearly.

the lesion appears to be a true congenital aorto-azygos fistula. Steinberg *et al.* (1963) reviewed congenital A.V. fistulae and described eight cases. Three of these were coronary A.V. fistulae. One was between the right scapular artery and vein, one between the right thoro-cervical trunk and vein, one in the scalp, one between the left femoral artery and vein, and in the same patient, between a lumbar artery and vein. This last case was in a five-month-old infant with Turner's syndrome. This is the only case which showed a communication between the systemic artery and azygos vein since the lumbar artery communicated with an ascending lumbar and azygos vein as well as the inferior vena cava.

It is interesting that all these cases presented to cardiologists because of the unusual murmurs and it was only systemic angiography which finally established the true diagnoses. In all three cases the true

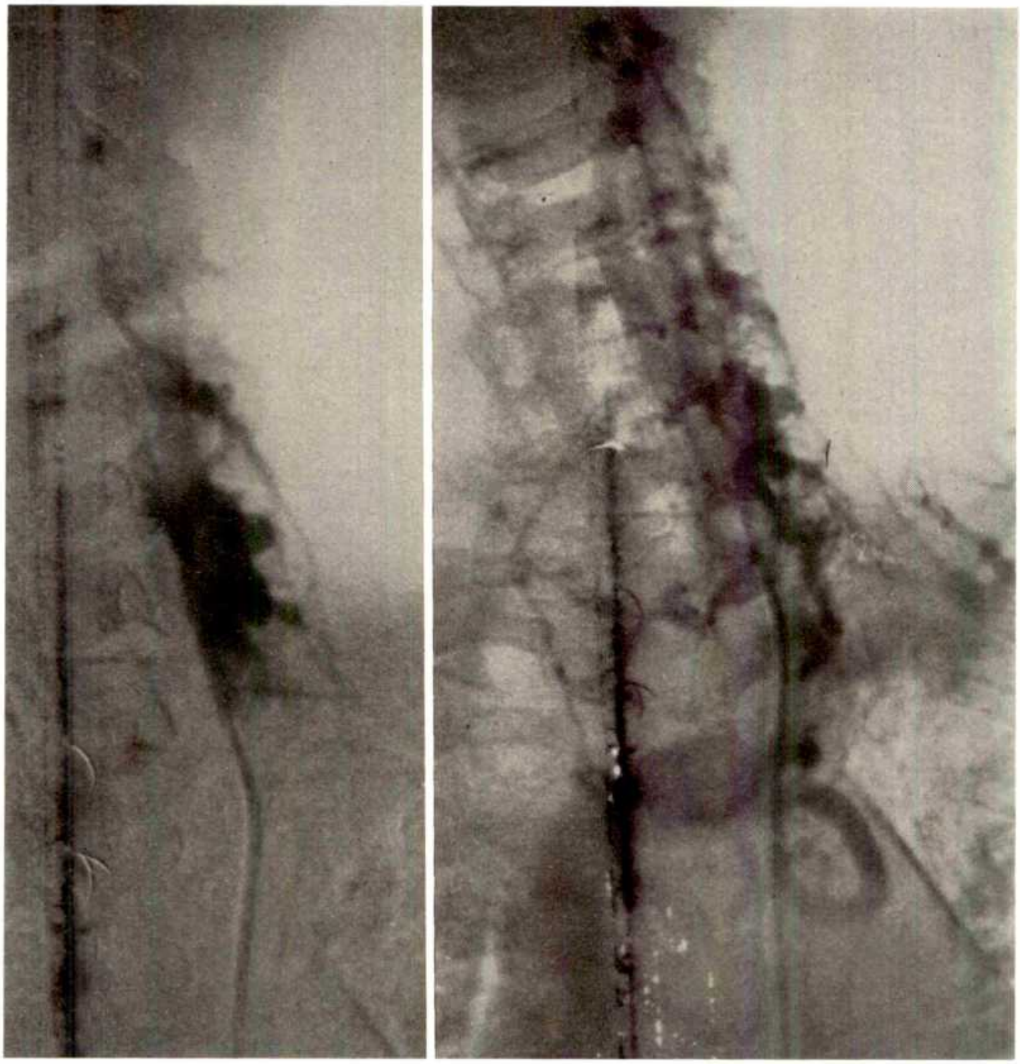

FIG. 6.

Selective injection of vertebral A.V. fistula. (A) Early film showing dilated vertebral venous plexus. (B) Serial film showing drainage to the innominate vein and superior vena cava.

nature of the lesions was not apparent until arch aortography was performed and even then it was only careful examination of the arch aortogram films which led to the more diagnostic selective angiographic procedures.

ACKNOWLEDGMENTS

Our thanks are due to Dr. Edwin Besterman who referred these cases for arch and systemic angiography.

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Myxofibrosarcoma: a pathologico-anatomical, microangiographic and angiographic correlative study of eight cases

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ABSTRACT

A correlated angiographic, microangiographic and histological study of eight myxofibrosarcomas is presented. Myxofibrosarcoma is a very recently described type of malignant soft tissue tumour characterized by a mucoid and nodular appearance, predominantly arising superficially in the extremities and trunk in elderly people. Microscopically, the lobulated and myxoid tumours in the present series showed a characteristic plexiform network of fine capillary-like vessels and occasional wide, sinusoidal, angulated vessels. On plain radiographs they were all dense and well demarcated. Angiographically the tumours appeared highly vascular, with irregular tumour vessels often arranged in a patchy or nodular fashion. All revealed signs of a rapid circulation. The microscopic and angiographic appearances were correlated, in two cases utilizing microangiography. In the presence of a superficially located tumour with high density on plain radiographs, marked vascularity, patchy or nodular opacities, and signs of rapid circulation on angiogram one should suspect this diagnosis.

Myxofibrosarcoma is a malignant soft tissue tumour, recently defined as an entity and believed to adhere to the general category of fibroblastic and histiocytic malignant soft tissue tumours. It is characterized by a mucoid and nodular appearance with a distinct, coarse plexiform capillary pattern. It is chiefly seen subcutaneously in the extremities and trunk of elderly people (Angervall *et al.*, 1977).

Other soft tissue tumours of predominantly myxoid character are myxoma (Stout, 1948; Enzinger, 1965; Ireland *et al.*, 1973; Kindblom *et al.*, 1974b), myxoid liposarcoma (Stout, 1944; Enzinger and Winslow, 1972; Kindblom *et al.*, 1975) and extraskeletal myxoid chondrosarcoma (Enzinger and Shiraki, 1972). Histological angiographic and microangiographic studies of intramuscular myxoma and liposarcoma have been reported. On plain radiographs the intramuscular myxomas and the myxoid liposarcomas are both very dense but are angiographically clearly distinguishable since intramuscular myxomas are poorly vascular and the myxoid liposarcomas highly vascular compared with muscle tissue (Kindblom *et al.*, 1974b and 1975). Extraskeletal myxoid chondrosarcoma has not been studied angiographically, as far as we can gather from the literature.

Experience with the angiographic appearance of various soft tissue tumours is limited since only a few large, morphologically well-defined series have been reported (Stener *et al.*, 1969; Kindblom *et al.*, 1975). A deepened knowledge, obtained by correlating morphological and angiographic findings in larger series, is therefore needed for the evaluation of the usefulness of angiography in the pre-operative investigation of various soft tissue tumours.

The present report describes a pathologic-anatomical, microangiographic and angiographic correlative study of eight myxofibrosarcomas.

MATERIALS

The material for this study consisted of fresh tissue, histological blocks and slides, clinical histories and radiographs from eight patients with myxofibrosarcoma studied by angiography. Three were collected by review of a National Swedish series of soft tissue sarcomas reported to the Swedish Cancer Registry between 1958 and 1965. The other five were consecutive cases studied by angiography at the Department of Radiology, Sahlgren's Hospital, Gothenburg, Sweden, between 1966 and 1976. In all cases both angiograms and plain radiographs were available.

METHODS

Histological and microangiographic methods

From the tissue blocks new 5 μ sections were cut and stained by the haematoxylin-eosin and haematoxylin-van Gieson methods. Weigert's elastin stain was used for studying elastic tissue in the tumour vessels. In selected cases Gordon's silver impregnation was used for the demonstration of reticulin fibres. Alcian blue staining at pH 2.5 and 0.5 (Chroma-Gesellschaft), toluidine blue stains at pH 4.0 and 0.5 (E. Merck, Darmstadt) with and without prior digestion with testicular hyaluronidase and the "CEC-method" (Scott *et al.*, 1965) were applied to aid the detection of glucosaminoglycans (Angervall *et al.*, 1973; Kindblom *et al.*, 1975). Histologically the tumours were divided into four grades according to the degree of tumour cellularity, atypia and prevalence of mitotic figures (Angervall *et al.*, 1977).

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Two myxofibrosarcomas (Cases 4 and 6) were prepared for a correlated microangiographic and histological study mainly according to the methods described by Angervall *et al.* (1964a and b) and Kindblom *et al.* (1975). In these two cases only tumour tissue blocks were available and survey microangiograms of slices of wet tissue could not be prepared.

TABLE I

Age and sex of patients, tumours site and size, and histologic grade of eight angiographically studied myxofibrosarcomas

Case no.	Age (years)	Sex	Tumour site	Size (cm)	Histologic grade	Follow-up period (years)	Results
1	79	M	Upper arm, left	8	IV	1¼	Recurrences after 3 and 4 months, died with metastases after 1 year and 3 months
2	51	F	Elbow, right	9×5×3	III	3	Alive and well
3	24	M	Calf, left	2.5	I	5	Alive and well
4	65	M	Leg, left	6×6	III	11	Recurrences after 7 and 10½ years, alive and well
5	63	M	Upper arm, left	10	IV	2½	Alive and well
6	69	M	Thigh, right	8×6	II	2½	Died with metastases to paravertebral tissue and bronchopneumonia (autopsy performed)
7	72	F	Knee, left	14×8×8	IV	1	Alive and well
8	73	F	Buttock, left	21×9	IV	Seven months	Alive and well

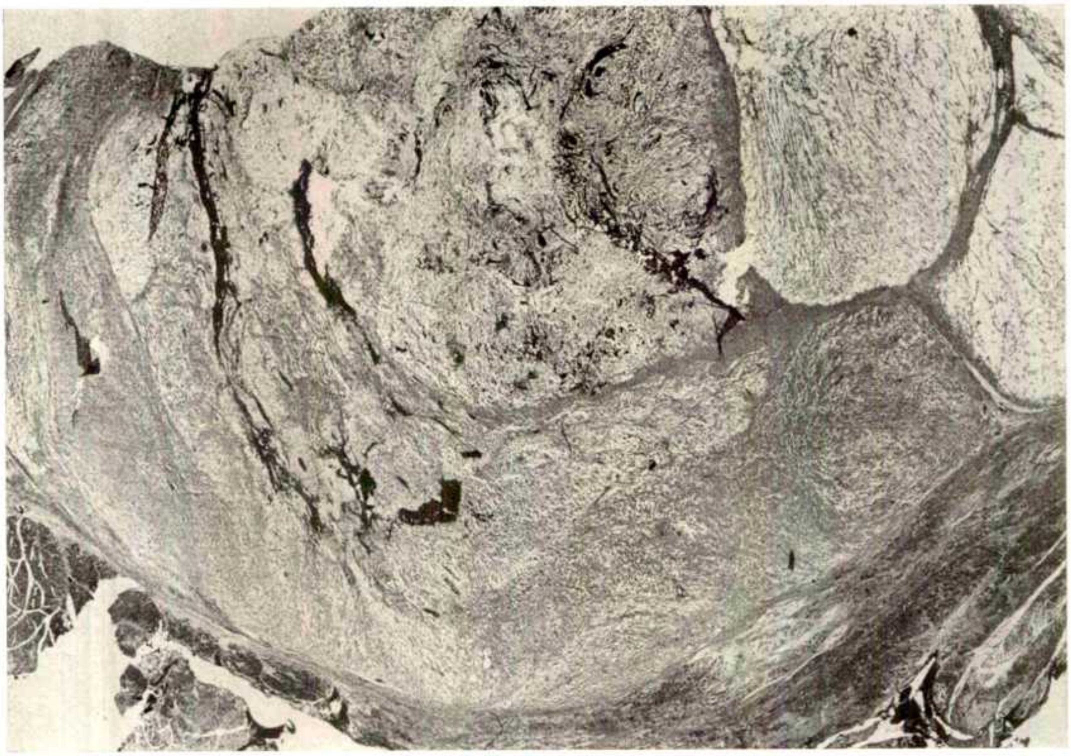

Fig. 1.

Subcutaneous myxofibrosarcoma with a characteristic myxoid and nodular appearance reaching the underlying muscle tissue (bottom). H & E, ×5.

Clinical radiological methods

Plain radiographs were assessed regarding the radio-opacity and localization of the tumour in relation to surrounding skin, subcutaneous tissue and muscle. Most angiograms included at least two different projections using a rapid film changer. The films in all but one case covered the whole circulation time, including the venous phase. The vascularity of the tumour was studied and compared with that of the surrounding subcutaneous and/or muscle tissue. Tumour vessels were examined and described as irregular if meandering in abnormal directions, if having a tortuous or curved course, and if varying in width or lacking an ordinary diminishing calibre. Signs of a rapid circulation in the tumour, manifested by the early appearance of isolated veins draining the tumour or by opacification of the tumour before the surrounding tissue, were recorded. Opacification of the tumours was compared with surrounding subcutaneous and/or muscle tissue. The size, shape and location of the tumour was estimated from plain radiographs and angiograms, and compared with the clinical estimation and the actual appearance of the tumours found on gross examination of the specimen. The relationship between the feeding arteries of the tumour and other vessels was studied by stereoscopy whenever possible.

RESULTS

CLINICAL DATA

The clinical information is summarized in Table I.

Age and sex

Most patients were elderly, six of them over 63 years of age. The youngest patient, aged 24, had a small tumour in the left calf, and the oldest, a 79-year-old woman, a tumour located on the dorsal aspect of the left elbow.

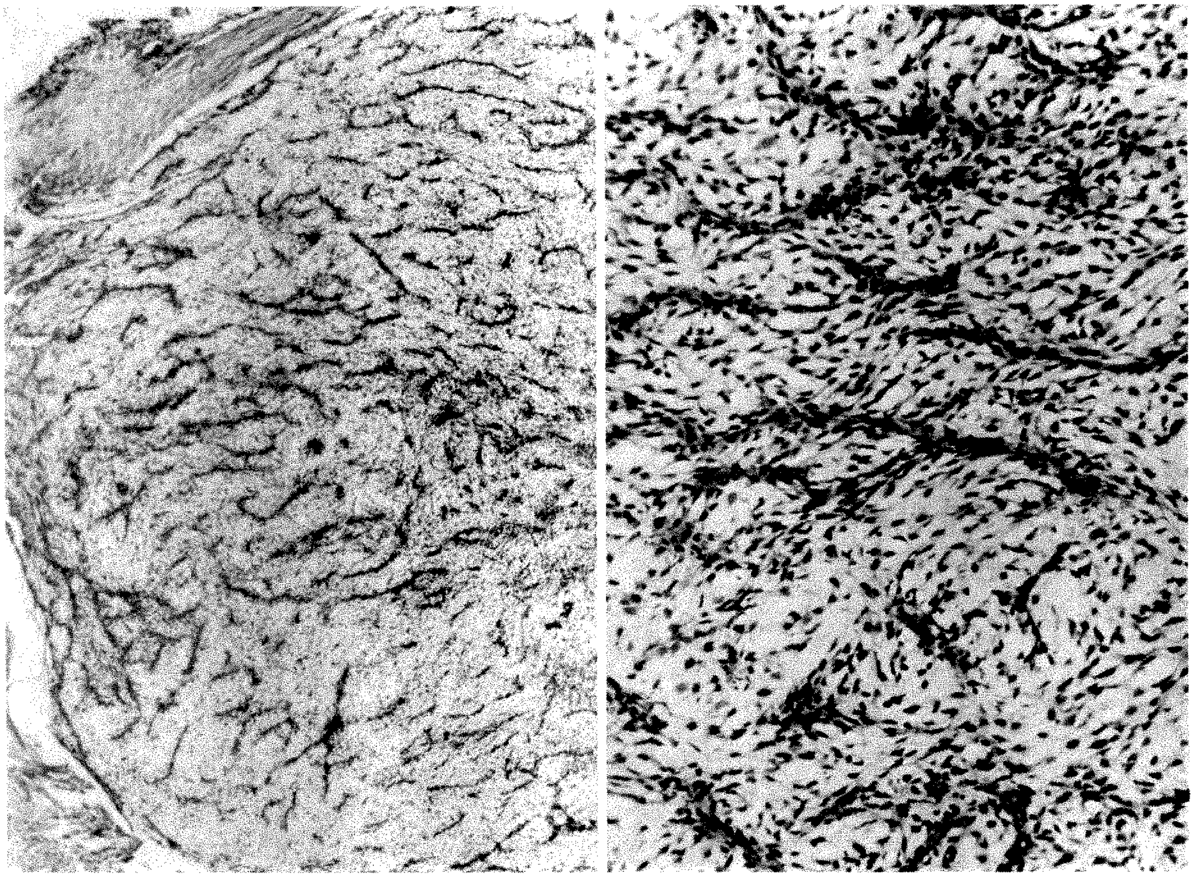

FIG. 2. FIG. 3.

Tumour nodule with a prominent plexiform capillary network. The tumour tissue is composed of an abundant mucoid matrix and slightly polymorphic spindle-shaped cells. H & E, ×30 (Fig. 2), ×120 (Fig. 3).

Anatomical location

All the eight tumours occurred in the extremities. Three affected the upper limbs, and five the lower extremities. Four of the eight tumours were entirely located in the subcutaneous tissue, and four partly or wholly inter- or intramuscular.

Treatment and prognosis

All of the eight patients were treated by local excision of the tumour. The follow-up period ranged between seven months and 11 years. Two patients experienced recurrences, in one of them the first recurrence appeared as late as seven years after the primary operation. Two patients died with metastatic spread one year and three months, and three-and-a-half years after the primary operation. The other six patients are alive and without signs of tumour after seven months to 11 years.

PATHOLOGY

Gross findings

The tumours were oval or spherical, with the largest diameter ranging between 2.5 and 21 cm. They were nodular in appearance, the nodules varying in size (Fig. 14D). Most tumours were soft to palpation and had a grey, glistening, mucoid appearance. Necrosis and haemorrhage were mostly found centrally. Grossly the tumours appeared well delineated.

Microscopic appearance

A characteristic feature of the tumours was the gross and microscopic nodularity, with fibrous septa separating areas of mucoid tumour tissue (Fig. 1). The cellularity, and appearance of the tumour cells, varied between different tumours, and to some extent

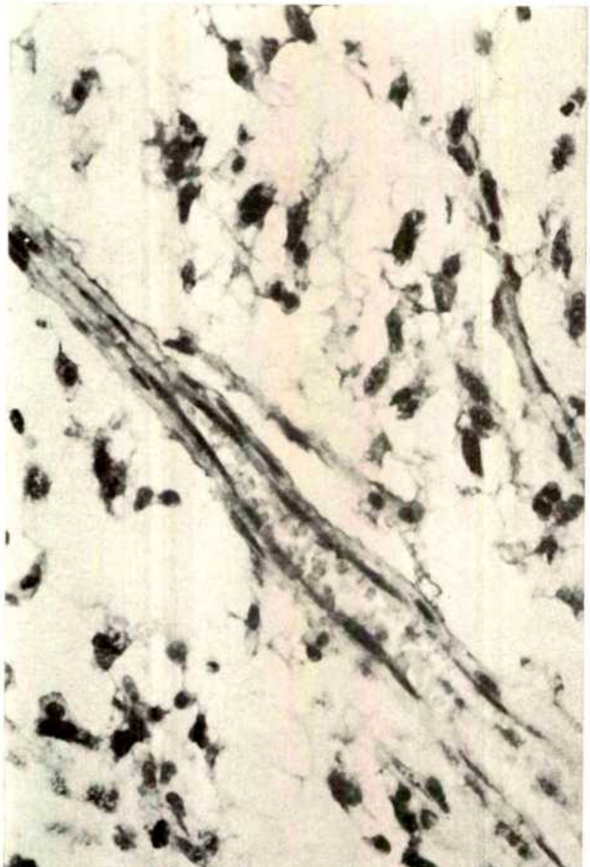

FIG. 4.

Blood-filled small capillary-like tumour vessels 7–20 μ in diameter lined by a single row of endothelial cells. H & E, × 3000.

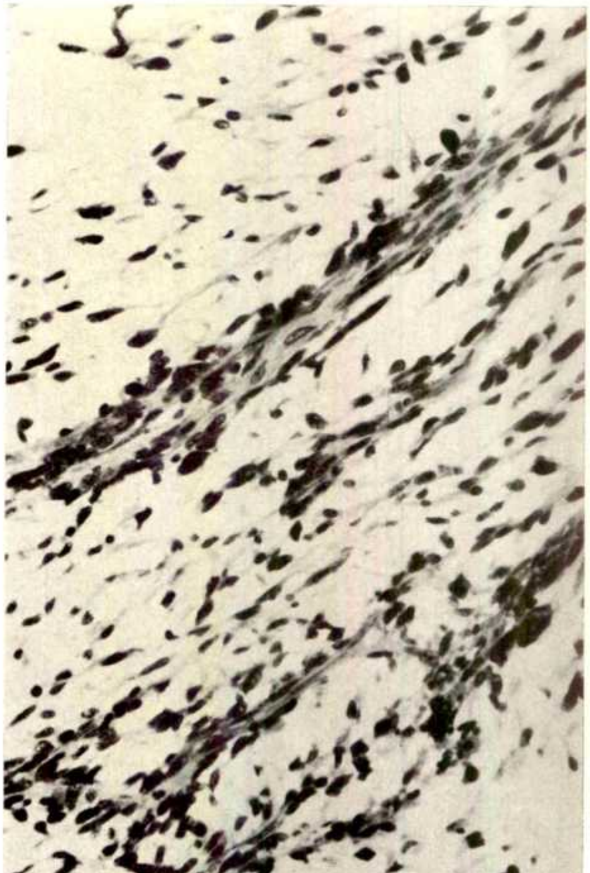

FIG. 5.

Condensation of moderately polymorphic tumour cells around delicate capillary-like vessels. H & E, × 120.

TABLE II

RADIOLOGIC APPEARANCE OF EIGHT MYXOFIBROSARCOMAS

				Appearances on angiograms			
					Rapid circulation		
Case no.	Histologic grade	Appearance on plain radiographs	Vascularity*	Tumour vessels	Early opacity	Early single veins	Opaqueness*
1	IV	Radio-opaque	More vascular	Irregular	Yes	Yes	More opaque
2	III	Radio-opaque	More vascular	Irregular	Yes	Yes	More opaque
3	I	Radio-opaque	More vascular	Irregular	Yes	Yes	More opaque
4	III	Radio-opaque	Much more vascular	Irregular	Yes	Doubtful	More opaque
5	IV	Radio-opaque	More vascular	Irregular	Yes	Yes	More opaque
6	II	Radio-opaque	Slightly more vascular	Irregular	Doubtful	Yes	Slightly more opaque
7	IV	Radio-opaque	Much more vascular	Irregular	Yes	Yes	More opaque
8	IV	Radio-opaque	More vascular	Irregular	Doubtful	Yes	More opaque

*In relation to the surrounding or underlying muscle tissue.

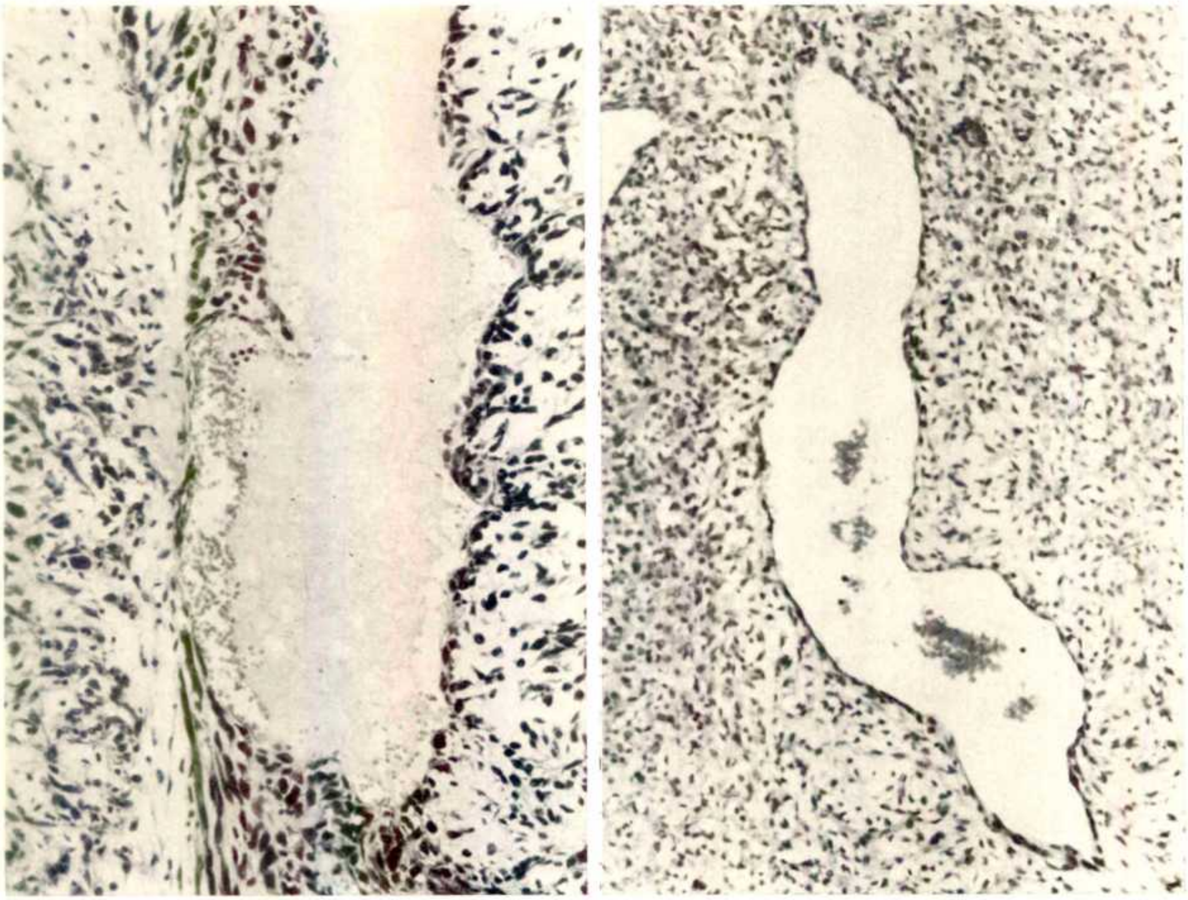

FIG. 6.

FIG. 7.

Wide, sinusoidal, angulated vascular spaces, about 200 μ in diameter, with tumour tissue irregularly protruding into the lumen. H & E, × 230 (Fig. 6), × 120 (Fig. 7).

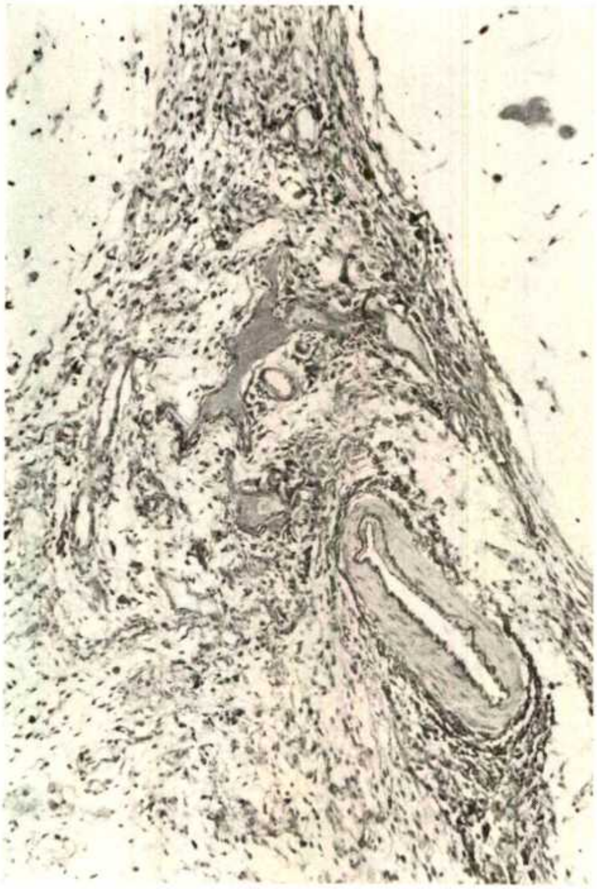

FIG. 8

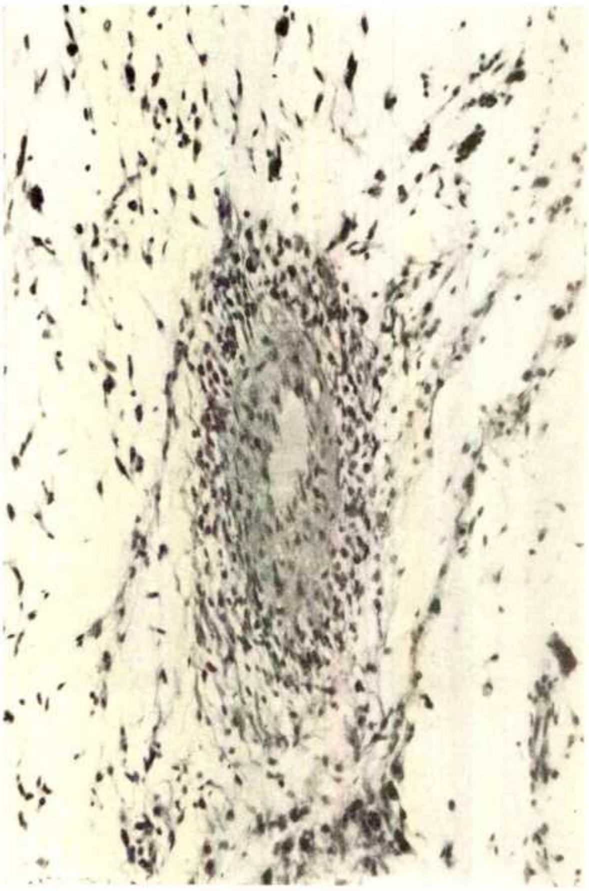

FIG. 9.

Subcutaneous tumour extension including a mature artery, numerous wide capillary-like vessels (Fig. 8) and some thick-walled, cellular vessels surrounded by a rim of tumour cells (Fig. 9). Weigert's elastin-van Gieson, ×90 (Fig. 8), H & E, ×120 (Fig. 9).

between different regions of any one tumour. Grade I and II tumours were sparsely cellular with a conspicuous mucoid matrix enclosing slender fibroblast-like cells showing only occasional mitotic figures. Grade III and IV tumours revealed also solid areas, some highly cellular, others with an abundant fibrous stroma. These tumours were composed of both fibroblast-like cells and more polymorphous, plump or rounded and occasionally multinucleated cells, with an abundant well-delineated cytoplasm, thus resembling histiocytes. Mitotic figures were frequently seen in grade III and IV tumours.

At pH 2.5 the mucoid tumour matrix stained with Alcian blue and it stained metachromatically with toluidine blue at pH 4.0. Neither the Alcian blue nor the toluidine blue staining was positive at pH 0.5. The positive stainings at the higher pH's were abolished by predigestion of the section with testicular hyaluronidase. The mucoid tumour matrix stained with Alcian blue up to 0.1 M $MgCl_2$. The result of these stainings indicated the presence of hyaluronic acid but not sulphated glucosaminoglycans (Kindblom and Angervall, 1975).

All the tumours revealed a characteristic vascular pattern. Numerous capillary-like vessels, most 5–10 μ in diameter, formed a striking plexiform network (Figs. 2 and 3). These vessels were lined by a single row of endothelial cells (Fig. 4) and enclosed by collagen fibres, occasionally with condensation of tumour cells around the vessels (Fig. 5). Within the mucoid nodules occasional wider sinusoidal vessels of primitive type were seen, often having an angulated course and showing tumour tissue protruding into the lumen (Figs. 6 and 7). Most were less than 100 μ in diameter. In one tumour (Case 3) the

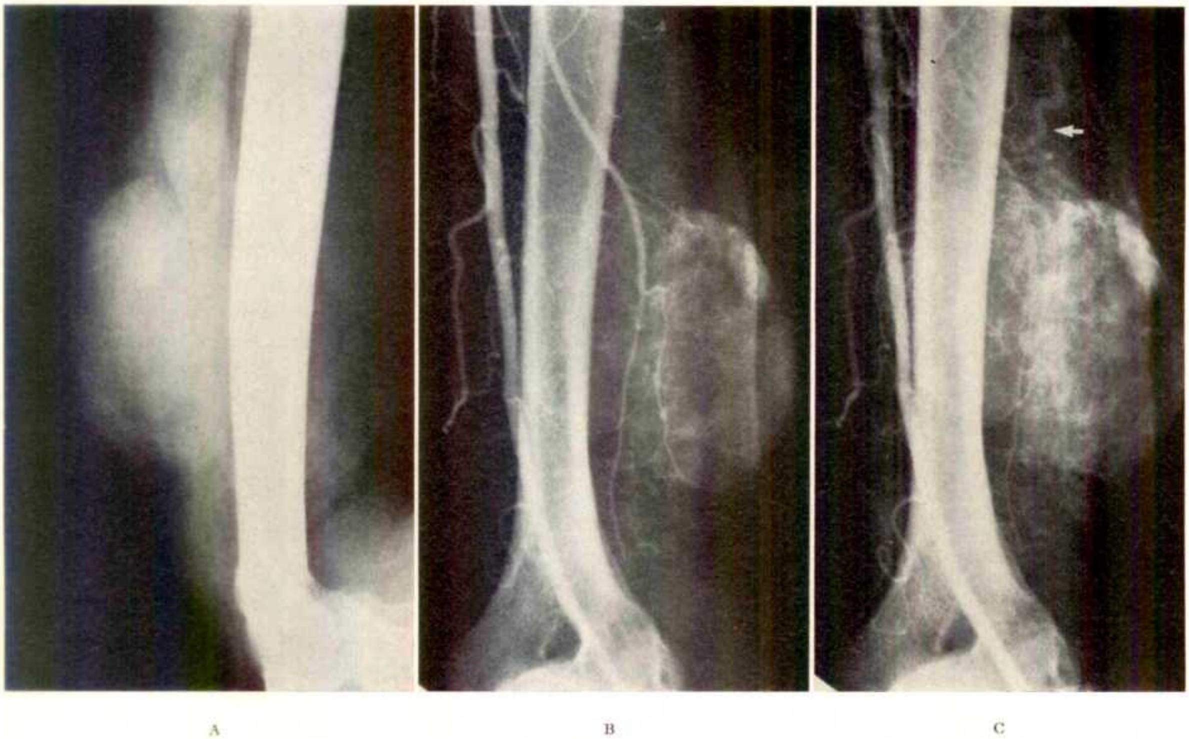

FIG. 10. *Case 1.*

A lobular myxofibrosarcoma in the upper arm.

(A) Plain radiograph showing a very dense, well demarcated superficial portion. The deep-seated portion of the tumour is obscured by the muscle tissue.

(B) Early arterial phase of angiography showing irregular small tumour vessels and patchy opacities.

(C) Late arterial phase. While the large arteries are still filled with contrast medium wide draining veins are seen (arrow). The opaque deep portion of the tumour is clearly visualized.

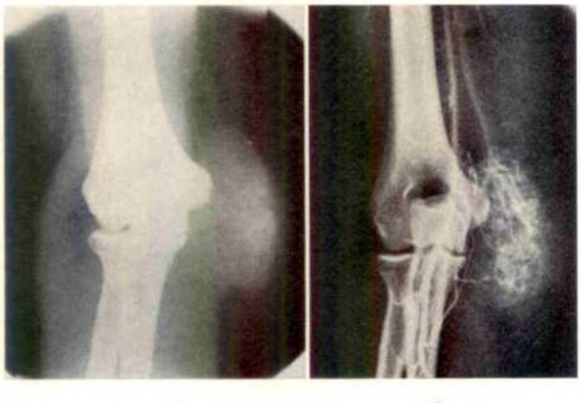

FIG. 11. *Case 2.*

Subcutaneous myxofibrosarcoma.

(A) Plain radiograph showing high density and sharp delineation of the tumour.

(B) Angiogram in the early arterial phase revealing developing patchy opacities and irregular tumour vessels.

plexiform capillary network was concentrated at the periphery of the nodules, while the centre contained larger thin-walled vessels up to 500 μ in diameter. Within the fibrous septa separating the nodules primitive capillary-like vessels of varying calibre, 10–200 μ in diameter, were seen. All tumours showed an infiltrative pattern of growth. Occasionally at the periphery a dense fibrous capsule-like structure was seen containing thin-walled vessels of a primitive capillary type, many more than 500 μ in diameter and occasionally up to 1·5 mm wide, in areas mingling with mature arteries and veins of roughly the same size. Tumours with a deep subcutaneous location close to the superficial fascia characteristically showed extensions along the fascial planes. These extensions contained small, rather thin-walled and cellular primitive vessels, lacking smooth muscle or elastic tissue up to 100 μ in diameter, with often a prominent perivascular condensation of tumour cells as well as occasional arteries and veins (Figs. 8, 9).

Radiology

The radiographic appearances on plain radiographs and angiograms are summarized in Table II.

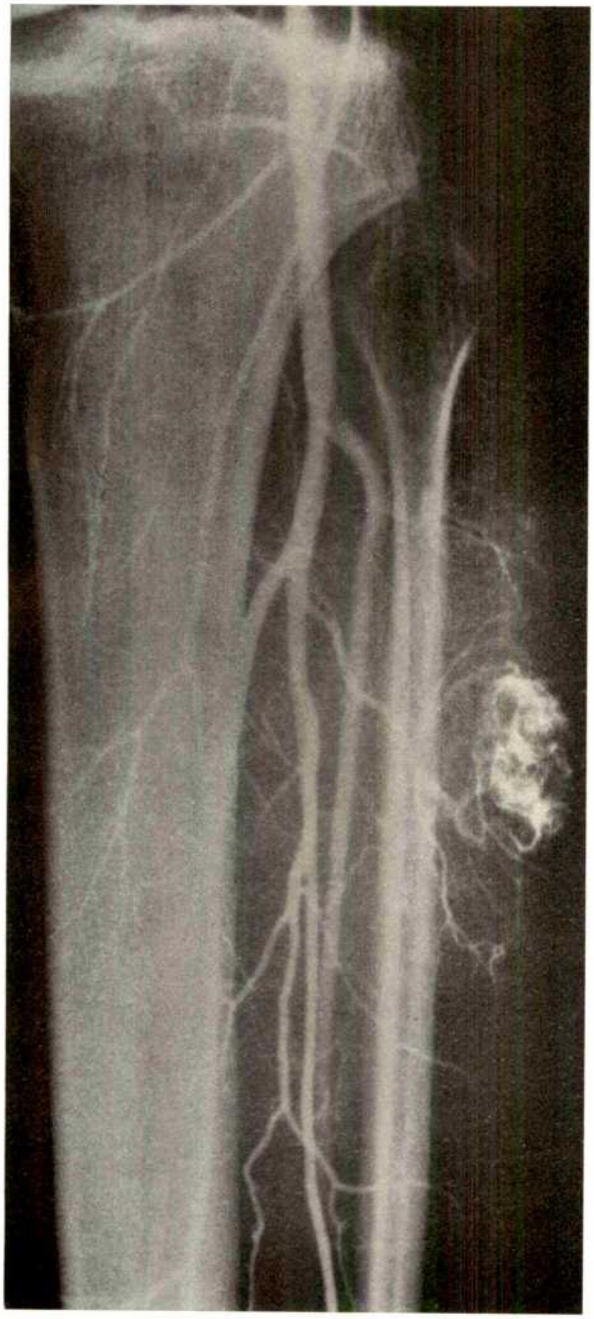

FIG. 12. *Case 3.*

Small myxofibrosarcoma located between the soleus and the lateral gastrocnemius muscles. Early opacification is evident.

All tumours were radio-opaque in the plain films The four tumours located entirely within the subcutaneous tissues were much denser than the surrounding fat and were therefore clearly defined (Figs. 10A, 11A, 14A). Tumour size could be readily estimated from the radiographs. The two wholly intra- or intermuscular myxofibrosarcomas had a slightly higher density than the surrounding muscle tissue but were not clearly delineated. One of the tumours growing both in subcutaneous and muscular tissues (Case 1) was distinctly lobulated, with a subcutaneous and another intramuscular portion. While the subcutaneous part was readily demonstrated, the deep-seated portion was unidentifiable. However, the angiograms distinctly outlined the deep portion of the tumour (Fig. 10).

Angiographically all tumours appeared more vascular than the surrounding or underlying muscle tissue (Figs. 10, 11, 12, 13, 14), two being extremely

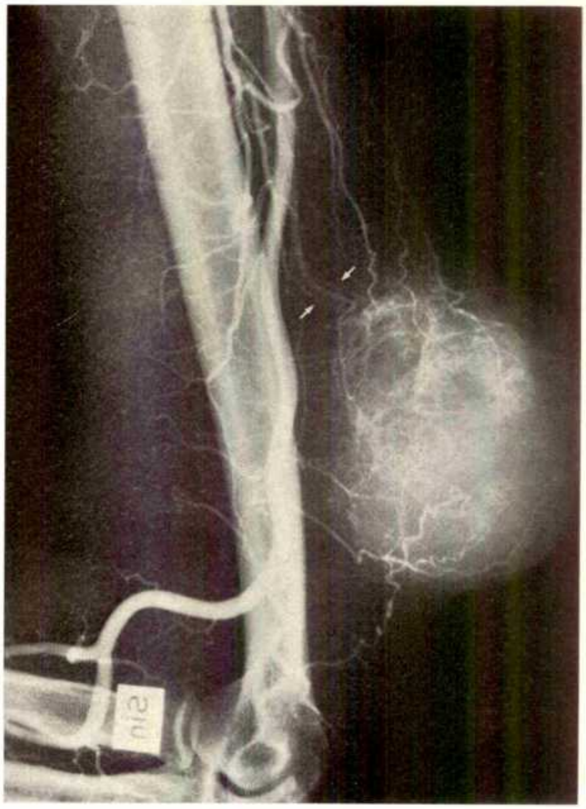

FIG. 13. *Case 5.*

Angiography of a very vascular subcutaneous myxofibrosarcoma with numerous curved and tortuous tumour vessels arranged in nests in the proximal part of the tumour. In contrast to the muscle tissue, the tumour is opaque and veins already drain the tumour (arrows).

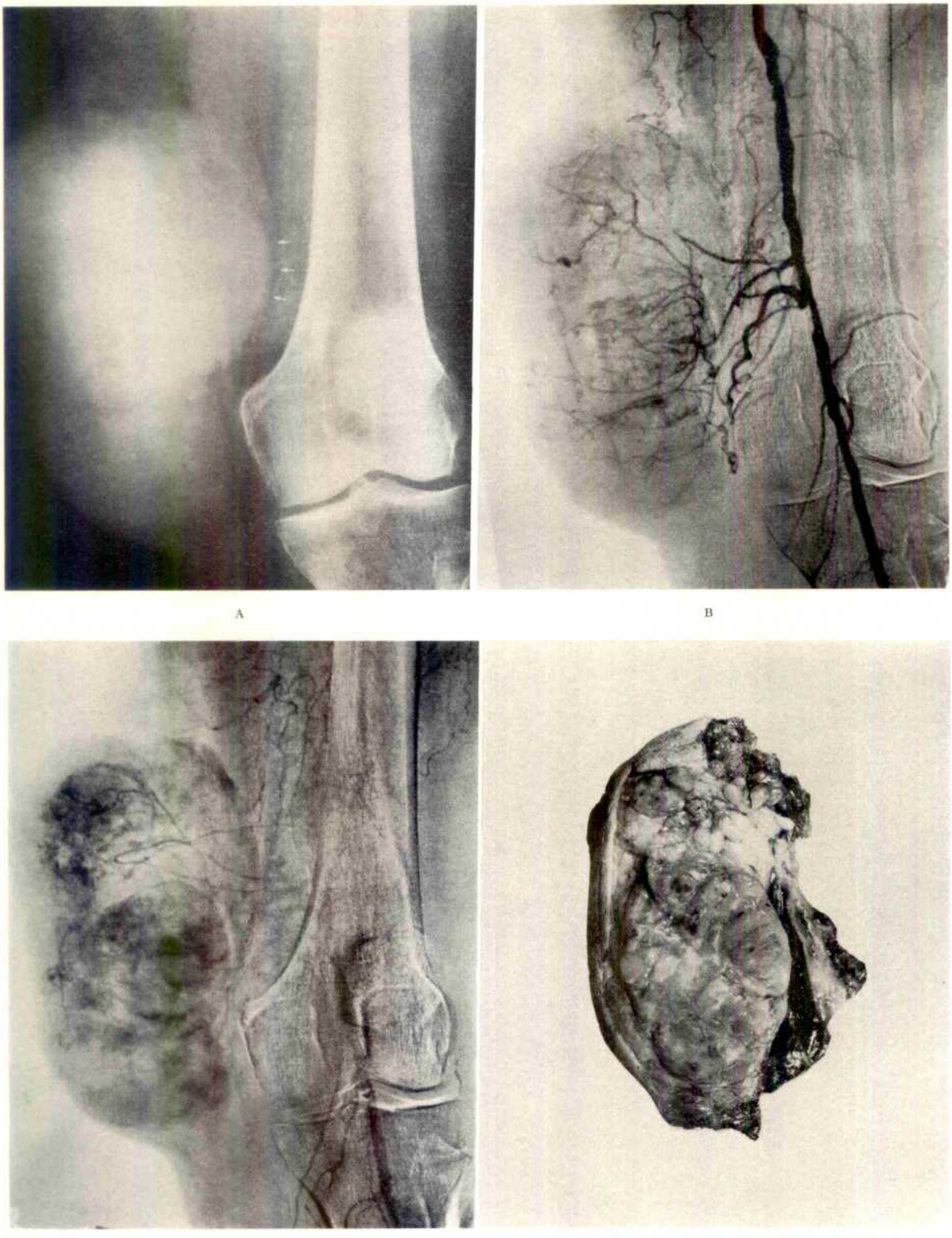

FIG. 14. *Case 7.*
A large subcutaneous myxofibrosarcoma of the medial, lower aspect of the thigh.
(A) Plain radiograph showing a dense, lobular tumour extending to the superficial muscle fascia (arrows) and compressing vastus medialis.
(B & C) Angiograms, subtraction technique.
(B) Irregular tumour vessels and developing opacification is evident in early arterial phase.
(C) Nodular and patchy opacification in late arterial phase.
(D) Section of the subcutaneous tumour which extends to the skin (left) and skeletal muscle (right). The microscopic extension of the tumour and the macroscopic nodular character correspond well with the appearance on the angiogram (C).

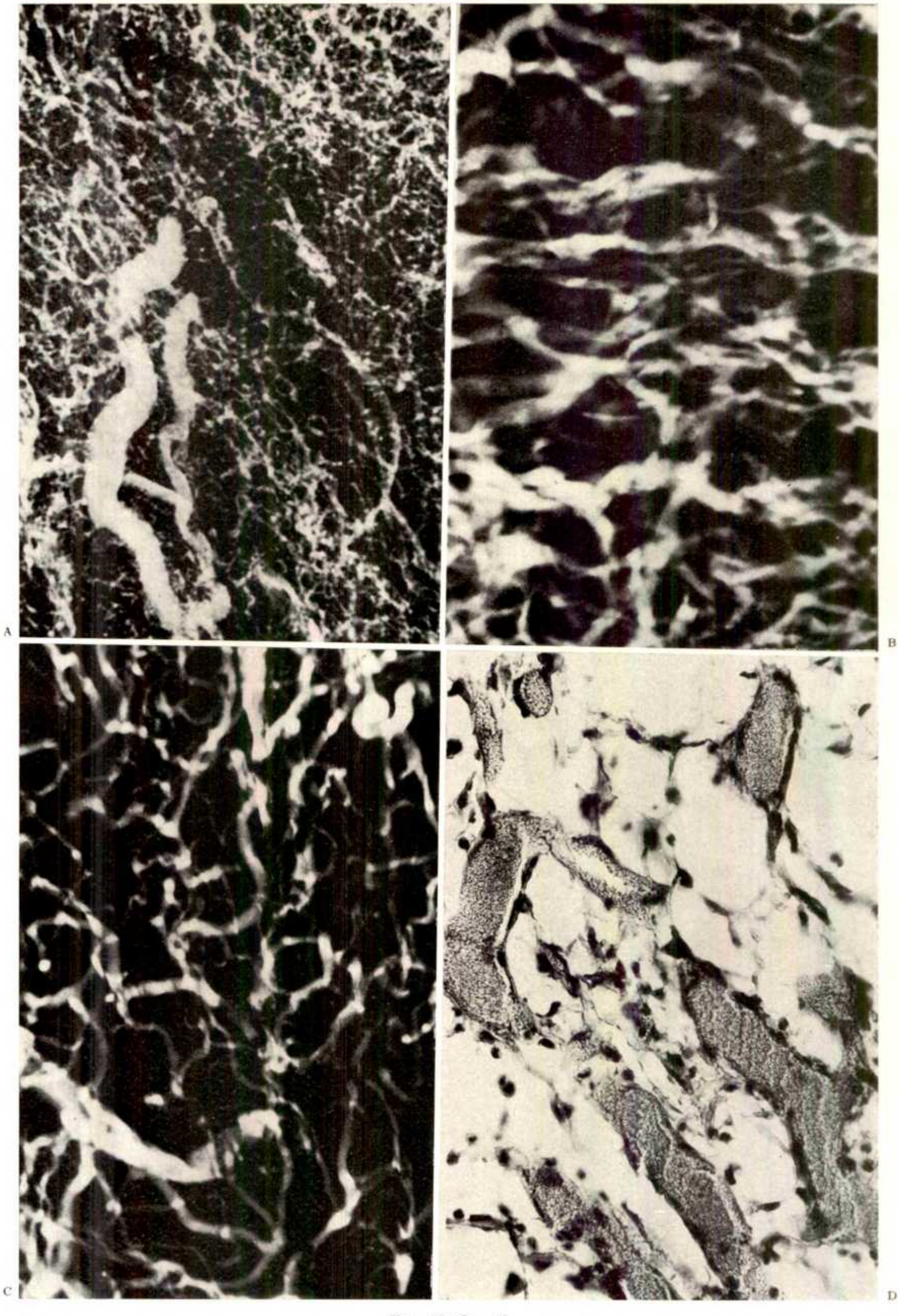

FIG. 15. *Case 6.*

(A) A low magnification (×30) photograph of a microangiogram of a 1 mm thick tumour slice showing the rich vascularity of the tumour. Only occassional large vessels, up to 250 μ in diameter, are individually discernible.

(B) A higher magnification (×150) of the same microangiogram shows a honeycomb-like network of small vessels.

(C) A high magnification (×225) of a 300 μ thick tumour section showing a fine meshwork of irregularly branching and anastomosing delicate vessels, the smallest 5 μ in diameter.

(D) Histological examination of the areas seen in (C) revealing numerous small capillary-like vessels filled with contrast medium (×300).

vascular. The poor vascularity of the subcutaneous tissue made the four superficial tumours stand out even more clearly than the deep-seated ones from the surrounding tissue. In all tumours, 1–2 mm diameter or smaller irregular vessels with a curved or tortuous course were found. These vessels often formed networks concentrated in small and mostly peripheral areas about 1 cm in diameter, giving the tumours a fine nodular appearance (Figs. 12, 13). Small and less vascular areas, often central, were seen in the tumour. In the later arterial phase small patchy or nodular opacities corresponding to the highly vascular areas with easily discerned irregular tumour vessels were seen (Figs. 10, 14). Rapid circulation was shown in all cases by the tumour becoming opaque before the surrounding or underlying muscle tissue and/or by early filling of single draining veins (Figs. 10, 13). The draining veins often appeared enlarged and ran a different course from the ordinary veins in the area. One tumour (Case 4) in the leg was supplied by a branch from the anterior tibial artery. Five seconds after contrast infusion, the supplying artery, 15 cm in length, was filled by contrast medium and filling of the tumour had started when contrast medium had just reached the proximal first centimetre of the main tibial arteries.

Microangiographic study

Paraffin-embedded tumour tissue blocks from Cases 4 and 6, prepared for microangiography, were first cut into 1 mm thick slices. Contact microangiograms of these slices examined with a light microscope showed the high vascularity of the tumour tissue. At a low magnification the microangiograms showed several irregular contrast-filled vessels, up to 200–300 μ in diameter, while the background appeared almost diffusely opaque (Fig. 15A). At higher magnification the smallest discernible vessels seemed to form honeycomb-like or network-like structures (Fig. 15B). Sections 300 to 400 μ thick were prepared from these areas. Higher magnification of the microangiograms of these thin sections clearly showed the network-like structure to be formed by irregularly dividing and anastomosing vessels, the smallest about 5 μ in diameter (Fig. 15C). Microscopic examination of these microangiographically studied areas disclosed the characteristic plexiform capillary pattern. The smallest vessels, 5–7 μ in diameter, were also filled with contrast medium (Fig. 15D).

DISCUSSION

The criteria of the diagnosis of myxofibrosarcoma have previously been described in detail in a report of 30 cases, five of which are included in the present series (Angervall *et al.*, 1977). The additional three angiographically studied cases fulfilled these pathologico-anatomical criteria.

All the eight myxofibrosarcomas had a common radiographic appearance. On plain radiographs they were very dense and well demarcated when subcutaneous, and angiographically highly vascular with irregular tumour vessels and rapid circulation. The high density on plain films may be related to their myxoid character. Intramuscular myxomas and myxoid liposarcomas, which also contain an abundant matrix composed of hyaluronic acid, have previously been shown to have a similar plain radiographic appearance (Kindblom *et al.*, 1975). However, myxoid liposarcomas are almost always deep-seated and myxomas predominantly occur intramuscularly or cutaneously (Stout, 1948; Ireland *et al.*, 1973; Kindblom *et al.*, 1974b; Kindblom *et al.*, 1975).

The correlated angiographic, microangiographic and histological study suggests that the irregular, curved and tortuous tumour vessels seen on angiograms correspond to the primitive, frequently angulated, wide, capillary-like or sinusoidal vessels seen microscopically and on the microangiograms. The fine patchy or nodular opacities in angiograms are likely to correspond to the highly vascular myxoid nodules with their conspicuous plexiform network of capillary-like small vessels found at microscopic and microangiographic examination. The rapid circulation, evidenced by early opacification, is probably due to the high vascularity of the tumours with thereby a low resistance to blood-flow. This might also explain the existence of early draining veins. However, the microscopic presence of peripheral, wide, primitive vessels mingling with arteries and veins, may also indicate the existence of arteriovenous shunts.

High vascularity, irregular tumour vessels, opacification and rapid circulation, as seen in all the present cases, have previously been taken as criteria of malignancy (Vogler and Deu, 1955; Strickland, 1959; Lagergren *et al.*, 1960; Lagergren and Lindblom, 1962; Sutton, 1962; Rösch, 1964; Steckel, 1966; Sterner *et al.*, 1969; Ney *et al.*, 1972; Kindblom *et al.*, 1974a and b; Kindblom *et al.*, 1975). It is noteworthy that this angiographic picture may also be seen in benign tumours which originate from highly vascular tissue, such as the hibernoma (Angervall *et al.*, 1964a) and haemangioma (Bartley and Wickbom, 1959) and in inflammatory lesions (Lagergren *et al.*, 1958; Kindblom and Gunterberg, 1977).

Myxoid liposarcoma and the present series of myxofibrosarcoma have similar radiographic appearances on plain films. The myxoid liposarcoma may be distinguished from the myxofibrosarcoma by the usually deeper location and lack of rapid circulation. Round cell and pleomorphic liposarcoma, also deep-seated, frequently show an angiographic appearance similar to that of myxofibrosarcoma with a rapid circulation. However, these liposarcomas frequently contain well-differentiated, lipoma-like areas which appear translucent on plain radiographs and poorly vascular on angiograms (Kindblom *et al.*, 1975).

The angiographic appearance of myxofibrosarcoma seems to be characteristic of malignant soft tissue tumours but not pathognomonic for this particular type. The often superficial location, high density, sharp demarcation on plain films, high vascularity, nodular structure and rapid circulation on angiograms however, should arouse suspicion of this diagnosis.

In one patient (Case 1) with a lobular myxofibrosarcoma in the upper arm, a deep-seated portion of the tumour undiscovered on clinical examination and plain X ray was shown at angiography. Pre-operative angiography of soft tissue tumours is not only of value in assessing possible malignancy but also the extent, relation to surrounding tissues and vascular supply of the tumour, all of which may be of importance for the surgeon in planning the operative procedure.

Prognostic conclusions cannot be drawn from this small series in which the follow-up period was five years or less in six of the eight patients. The previously reported series of 30 cases (Angervall *et al.*, 1977) showed a high frequency of recurrences and metastases were often seen in patients with a low differentiated tumour. This study indicated that simple enucleation should be avoided and that the treatement of choice is wide local excision.

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A method of visualizing and documenting pancreatic lesions by diagnostic ultrasound

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Abstract

A reliable method of visualizing and documenting pancreatic lesions by ultrasound is described. This method is valuable for the follow-up of varying types of pathology, and it may be applied to a wider range of lesions than pancreatic. It is simple and saves time and money for the ultrasonographer and is more easily interpreted by the clinician.

During the past three years, much attention has been focused on one of the remaining radiological blind spots, the pancreas. Some progress in visualization of the pancreas has been made by using diagnostic ultrasound with bistable machines (Duncan *et al.*, 1976; Filly and Freimanis, 1970; Gosink and Leopold, 1975; Smith *et al.*, 1975) and more recently with grey scale equipment (Doust and Pearce, 1976; Leopold, 1975).

In our experience of ultrasonic pancreatic scanning, the following factors improve the chance of success: (a) a sound knowledge of the pancreatic anatomy and anatomical relations; (b) a method of minimizing the masking effect of overlying gas-containing bowel; and (c) a system of recording and documenting the outline of the pancreas for comparison with repeat scans.

The manner in which we have come near to meeting these requirements is reported on here.

Patients and Methods

During the past four years we have scanned the pancreas in more than 250 patients.

The equipment used was an Ekoline 20 a bistable machine, with A and B modes, and an attached Tektronix B scan storage oscilloscope. A 2.25 MHz transducer produced satisfactory scans, recorded by means of a Polaroid camera. Scans were commenced in the transverse plane and, once the position of the pancreas has been established, longitudinal (Freimanis and Asher, 1970) and if necessary oblique scans were performed as well.

Observations

1. *Anatomy*

A study of the post-mortem appearance of the pancreas in 25 cadavers showed an enormous variation in the size, shape and position of the organ. The inclination of the long axis of the pancreas varied between 0 deg and 45 deg posterior to the coronal plane (Fig. 1).

Again, in the frontal view (Fig. 2) the axis varied between 0 deg and 45 deg above the horizontal plane. This information helps to determine the positions of transverse and longitudinal scans necessary to locate, demonstrate and demarcate the organ and also indicates that oblique scans may be helpful (Fig. 3).

2. *Visualization*

Bowel gas in stomach, duodenum and occasionally transverse colon often obscures most of the pancreas

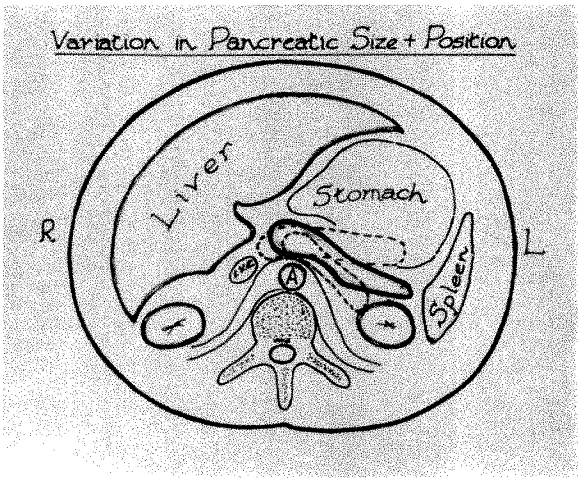

FIG. 1.

Transverse section through the abdomen demonstrating the variable shape, size and inclination of the pancreas to the coronal plane. The heavy outline is the standard anatomical position of the pancreas, the dotted lines show the variations in head, tail and angulation. "A" and "I.V.C." are aorta and inferior vena cava.

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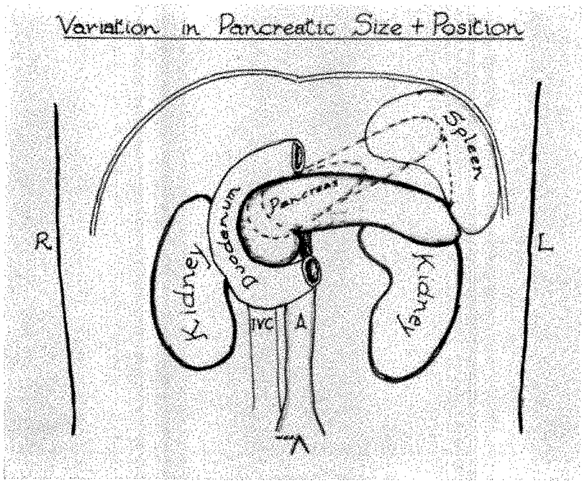

FIG. 2.

Frontal view of the abdomen with stomach removed showing the variable size and shape of the pancreas and its inclination to the horizontal plane. Note that the tail of the pancreas does not always reach the splenic hilum.

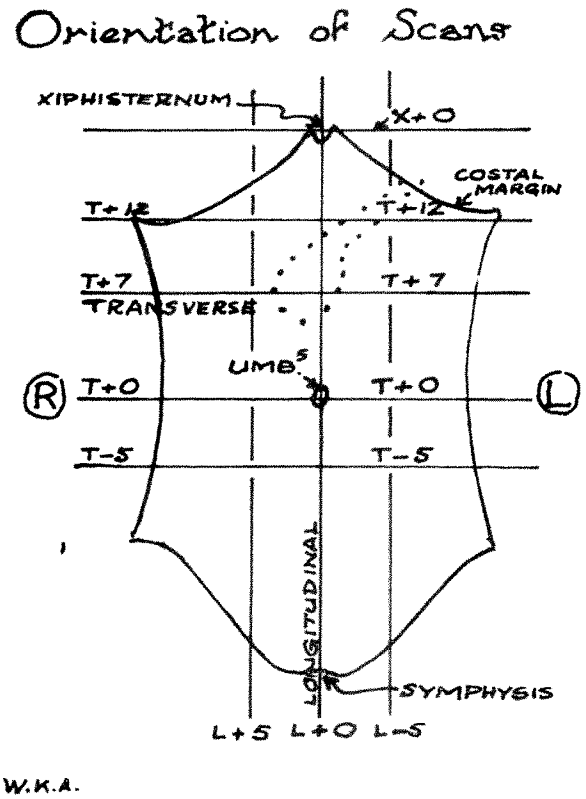

FIG. 3.

This illustrates the position of transverse and longitudinal scans used to demonstrate the pancreas. We have found the head of the pancreas most frequently situated at a level 7 cm above the umbilicus. T+7 indicates a transverse scan at this level.

TABLE I

WINDOW	PORTION OF PANCREAS REVEALED
Full gall-bladder	Head
Right lobe of liver	Head and body
Enlarged left lobe of liver	Body and occasionally tail
Gas-free stomach: soup or tumour of stomach	Tail
Enlarged spleen	Tail

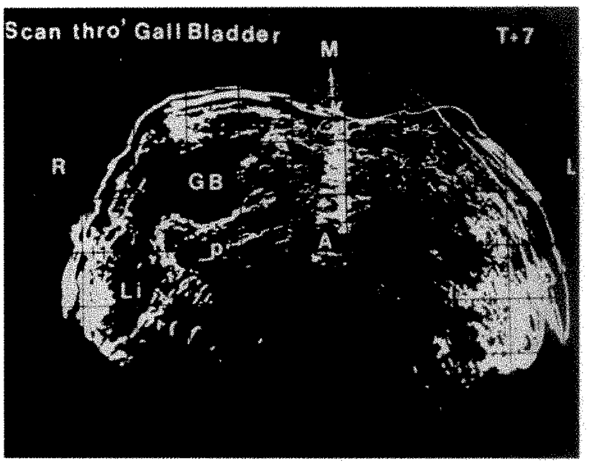

FIG. 4.

Good transmission of sound through the full gall-bladder (GB) demonstrates the head of the pancreas (P) well to the right of the midline. Overlying bowel gas in the midline (M) prevents visualization of the body and tail. "Li" represents the lateral limit of the right lobe of the liver, and "R" and "L" the right and left sides of the patient, in this transverse scan 7 cm above the umbilicus.

for the ultrasonographer. Various transsonic structures in the vicinity displace the bowel and provide useful "sound-windows" for displaying portions, at least, of the pancreas.

Listed in Table I are the various "windows" we have found useful, and the portions of pancreas revealed through them as illustrated in Figs. 4 to 6.

The success experienced in any particular patient is therefore dependent on the spatial relationship of the pancreas to surrounding solid and cystic organs

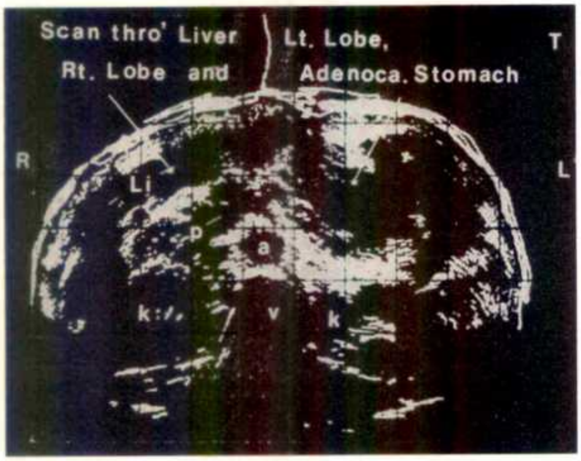

FIG. 5.

This transverse scan through the abdomen shows how right and left lobes of the liver (enlarged) and a solid tumour of the stomach have displaced all the bowel-gas from the area anterior to the pancreas. As a result, the pancreatic head (P) body and tail are visible. "A" represents the aorta, "V" the vertebral body, and "K" the kidneys.

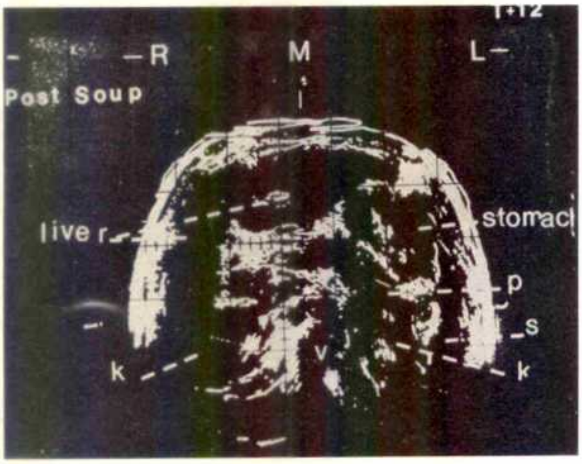

FIG. 6.

A transverse scan 12 cm above the umbilicus in a patient who had partaken of a bowl of soup immediately before the examination, illustrates how the fluid filled stomach enables visualization of the body and tail of the pancreas (P). The spleen (S), and both kidneys (K) are visible. An hour later, the stomach had emptied, and the pancreas was no longer visible.

(*e.g.* liver and spleen; and gall-bladder respectively). In addition, bowel gas is considerably reduced by starving the patient overnight before the examination. We have tried filling the stomach with water, but scans are not improved, as Filly and Freimanis (1970) and Doust (1975) have also found. In an attempt to prevent rapid emptying of the stomach, we have first given Hyoscine intravenously, also without success. Fortuitously, one patient had been given soup, through which the tail of pancreas was clearly seen.

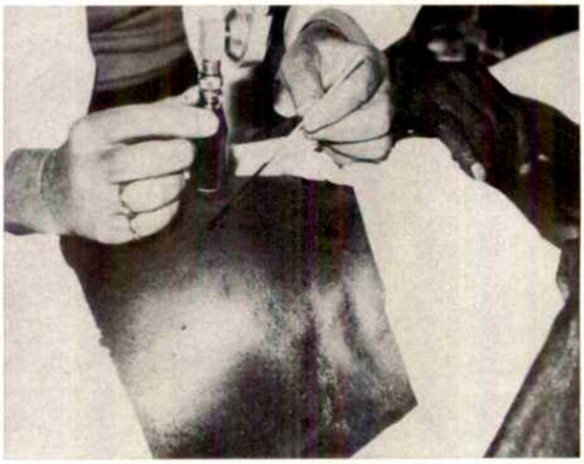

FIG. 7.

The method of marking the border of the pancreas on the overlying skin can be seen. The transducer, positioned over the edge of the organ in the A.P. direction, is lifted vertically, and the centre of its impression marked using the orange stick dipped in Gentian Violet.

Scans should be carried out before barium investigations (Leopold and Asher, 1971) as the latter prevents the transmission of the ultrasound beam.

In 1976, 143 patients were referred for ultrasonic examination of the pancreas. In 43 (30%) the entire pancreas was visualized, and in 39 (27%) the head and body were seen. The head alone was perceived in 14 (10%) and body and tail in 13 (9%). The body by itself was seen in eight (6%) and the tail exclusively in three (2%).

The pancreas could not be seen in 23 patients (16%). Eighteen of these had not been starved as instructed, while two had been given barium on the day prior to examination. Of the three remaining patients, one could not be scanned through dressings covering most of the abdomen, and the other two had ascites on which bowel floated.

3. *Documenting pancreatic size and shape*

We have developed a cheap, simple and reliable method for documenting pancreatic size and shape, with reference to various anatomical landmarks.

As illustrated in Fig. 7, the transducer is positioned in A.P. direction, over the right and then the left borders of the pancreas in successive transverse scans 1 cm apart. To mark the positions of the borders in each scan, the transducer is lifted

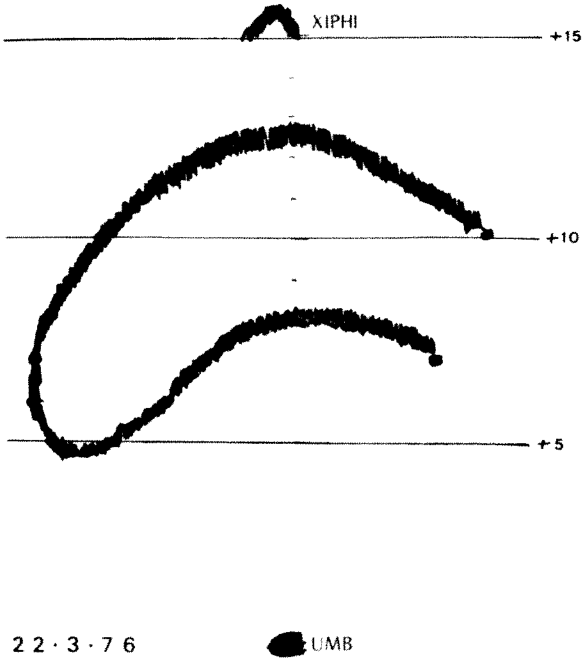

FIG. 8.

This is an example of the print obtained on a patient with acute pancreatitis. For ease of understanding, it has been pictured the right way round (although a reversed image is obtained), and the levels of the various scans indicated (with reference to the umbilicus). The xiphisternal and umbilical positions are marked in.

vertically; this leaves a circular inpression in the oil (coupling medium) on the skin. The centre of this circle is marked by using an orange stick dipped in Gentian Violet or ink. When the outline of the organ has been plotted, a line is drawn joining all the points on the right and also on the left sides of the gland. The umbilicus and xiphisternum are also marked in. A full size (though reversed image) contact print of the patient's abdomen is obtained by pressing a plain sheet of paper on to the wet inked outline (Fig. 8). More than one copy can be made.

DISCUSSION

Kreel *et al.* (1973) in a combined radiological and pathological study, have described the variable position of the head of the pancreas, and mention that the long axis of the organ can be horizontal or oblique. In addition, in our study of cadavers, we have found the inclination of the pancreas posterior to the *coronal* plane important in the ready identification of the organ. It is also noteworthy that the tail of the pancreas does not always reach the hilum of the spleen (Figs. 1 and 2). This is of help in mapping the outline of the pancreas on the skin. Various authors including Doust and Pearce (1976), have mentioned the use of the liver as a "sound window" for improving visualization of the pancreas. Extending this approach by the use of gall-bladder, spleen and gas-free stomach (aided by starving or filling with fatty soup) is of distinct benefit. Fatty soup is presumably far more effective than water at increasing the stomach emptying time.

If grey scale equipment is available, both kidneys can be used as "sound windows" with the patient lying prone, as described by Doust and Pearce (1976). Through the left kidney, the tail of the pancreas may be seen, especially if it is oedematous as in acute pancreatitis. The head of the pancreas can be visualized through the right kidney.

The system we have developed of documenting the pancreatic outline has several important advantages.

1. The outline of the pancreas is readily seen on the skin when the patient is returned to the referring clinician. Although the skin marking is temporary, a permanent print is retained.

Several authors, including Brascho (1974), have mentioned marking the limits of masses on the overlying skin, without specifying the marking method. We found that the oily coupling medium prevented various types of pens and "inks" from leaving any impression on the patient's skin.

The problem was finally overcome by using an orange stick dipped in Gentian Violet (or ink). It has proved cheap and reliable.

2. Ready comparison is available between this print and subsequent scans on the patient, and show progression or regression of the pathological process. These serial prints are of considerable importance in monitoring:

(a) Acute pancreatitis. Here correlation between pancreatic size and clinical and biochemical data can be obtained.

(b) Pseudocysts. The operation on a large pseudocyst is technically very difficult within the first five or six weeks of its detectable existence. This is because the wall is very thin and friable at first. On the other hand a pseudocyst which is enlarging rapidly is in real danger of rupturing intraperitoneally, with a possible fatal outcome for the patient. Serial mapping of pancreatic size is therefore of utmost importance.

(c) Pancreatic tumours. The response of the tumour to therapy can be demonstrated (Cohen, 1969).

3. The system is cheap and reliable, yet simple to perform. Time is precious and repeat scans are much more quickly performed when the position and angulation of the pancreas are known.

4. The prints obtained are self-explanatory and much more easily understood by the referring clinician than the Polaroid photographs of the scans.

5. The method is equally applicable to other organs (*e.g.* kidney, liver, spleen) and masses (*e.g.* abdominal and pelvic cysts, abscesses and tumours). Serial scans are very valuable here, too, showing alteration in size or shape with time, and therapy.

Conclusion

We have found that the use of various solid and cystic structures as "sound windows" improves visualization of the pancreas. Such structures include a full gall-bladder, right and left lobes of the liver, gas-free stomach and an enlarged spleen.

In addition, we have developed a method of "mapping" the pancreatic outline. This "map" is easily interpreted by the clinician, and useful for follow-up (particularly in pseudocysts of the pancreas).

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Book review

Strahlentherapie—Radiologische Oncologie. Edited by E. Scherer, pp. 800, 272 illus., 1976 (Berlin, Springer Verlag), DM160.

This book is designed to give the radiotherapy trainee a survey of radiotherapy with special references to its place in the treatment of malignant disease. The opening chapters are concerned with radiation physics, general methodology and treatment planning. A chapter on the biological basis of radiotherapy deals mainly with the results of experiments in cellular and molecular radiobiology. A short chapter on radiotherapy of benign conditions precedes the main part of the book which is devoted to malignant disease of various organs and systems.

The multidisciplinary approach is emphasized and clinical aspects are given in greater detail than in some other radiotherapy texts. The full discussions of the value of radiotherapy and its employment as a curative or palliative measure also state the position of surgical and medical treatment and deal with the question of integrating the different treatment methods. Radiation techniques are outlined and the reader is referred to original papers for finer details. There is a comprehensive list of references from the international literature at the end of each chapter. The text is clearly written, well set out and amply illustrated.

Professor Scherer and his 24 co-authors have succeeded in producing a book which will be a valuable source of information and a guide to further reading, not only for the radiotherapy trainee but for anyone concerned with the treatment of patients suffering from cancer.

M. Hulbert.

1977, *British Journal of Radiology*, *50*, 893–901

DECEMBER 1977

Interaction of hyperthermia and radiation: the survival surface

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ABSTRACT

The interaction of hyperthermia and radiation on cell survival is illustrated by the increase in sensitivity to radiation caused by hyperthermia and the increase in sensitivity to hyperthermia caused by radiation. A method of expressing the total response to a combination of these two agents by means of a survival surface in three dimensions is explained and discussed. A simple mathematical model of the surface is formulated in which a first order interaction term is separated from the two terms representing unperturbed radiation survival and unperturbed hyperthermia survival.

An experiment is described in which survival data points were obtained for 77 combinations of radiation and hyperthermia doses in the form of a matrix. These data points are plotted as 11 radiation survival curves and seven hyperthermia survival curves. The results are also analysed to give the parameters of the survival surface model. The model with its three components is shown to be a good approximation to the experimental results.

The effects of a great many agents on the response of cells to radiation have been extensively studied by determining the differences in radiation response between the normal population and the populations which have been affected by the agents. Less commonly the effects of radiation on the response of cells to the agents have been studied. These two types of studies taken together constitute a study of the interaction between the agents and radiation.

It has been known for some time that hyperthermia and radiation interact in their effects on cell survival (Belli and Bonte, 1963; Ben-Hur *et al.*, 1972, 1974; Robinson and Wizenberg, 1974). In none of these papers is the relationship between the sensitized hyperthermia response and the sensitized radiation response examined. In fact the experimental designs usually have not been appropriate for such an examination. The experimental studies and theory presented in this paper were designed to allow a closer analysis of the interaction to be made.

A few preliminary experiments are described as examples to illustrate the theory and the main experimental design. An explanation is then given of a way in which the interaction of two stimuli can be examined by mapping the response over a co-ordinate system which consists of orthogonal functions of the stimuli, generating a response surface. The determination of the response surface, while not conceptually difficult, presents practical problems.

Since it is probable that the response of the system changes with time and different culture conditions, it is preferable to determine the surface quickly and with as little change in experimental conditions as possible. The matrix type of experiment described fulfils these requirements and facilitates the analysis of the interaction phenomena.

An approximate theoretical model is developed to describe the surface as experimentally determined. The model allows analysis of the effects into three separable components representing the radiation, the hyperthermia, and the interaction effects. The analysis should be of interest since hyperthermia may in the future be an agent with an increasing role in the treatment of cancer. In addition, the interaction phenomena deserve careful characterization since they may throw light on the mechanisms of effects of both radiation and hyperthermia.

MATERIALS AND METHODS

Chinese hamster ovary cells were maintained in exponential growth as monolayers in plastic flasks. Hams F10 supplemented with 2 mM glutamine and 15% calf serum and buffered with a 5% CO_2-air mixture yielded plating efficiencies of 60 to 75%. Hams F12 supplemented with non-essential amino acids, 2 mM glutamine and 15% calf serum and buffered with 20 mM Hepes buffer yielded plating efficiencies of 50 to 65%. Stock cultures were maintained on antibiotic-free medium. Experimental media were supplemented with Gentamycin.

Asynchronous cells were harvested from a monolayer at a cell density of 8×10^4 cells/cm^2 by trypsinization with a Trypsin-EDTA mixture. The cells were either treated immediately in suspension or allowed to plate out for two hours at 37°C prior to treatment.

Irradiation was by a therapy ^{60}Co source. Where cells were irradiated in glass tubes, local effects of the walls on radiation dose have been ignored. Heating was by immersion in a waterbath (Grant SX-35) in which the temperature stability was ± 0.02°C.

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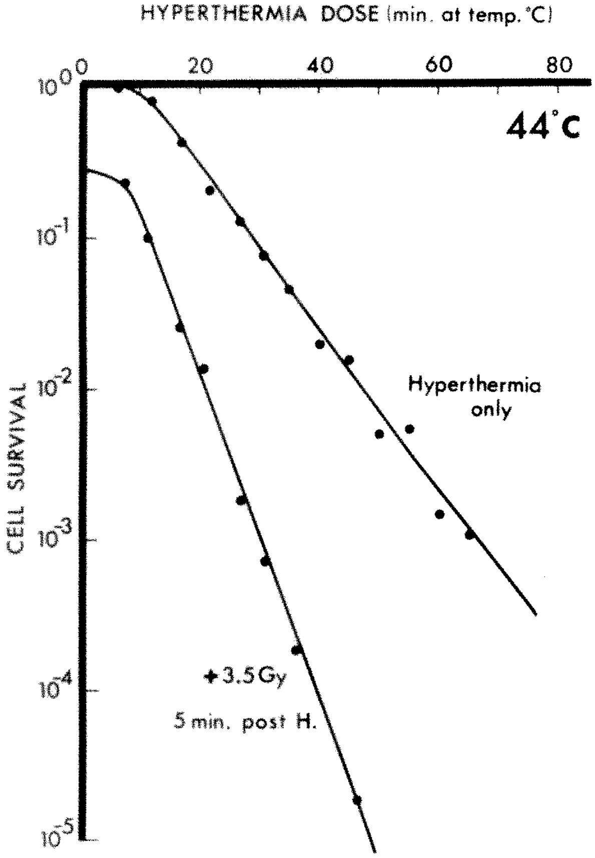


Fig. 1.

CHO cell hyperthermia survival curves after hyperthermia at 44°C either alone or followed 5 min later by 3.5 Gy of ^{60}Co radiation at room temperature. The data points show the results of a single experiment.

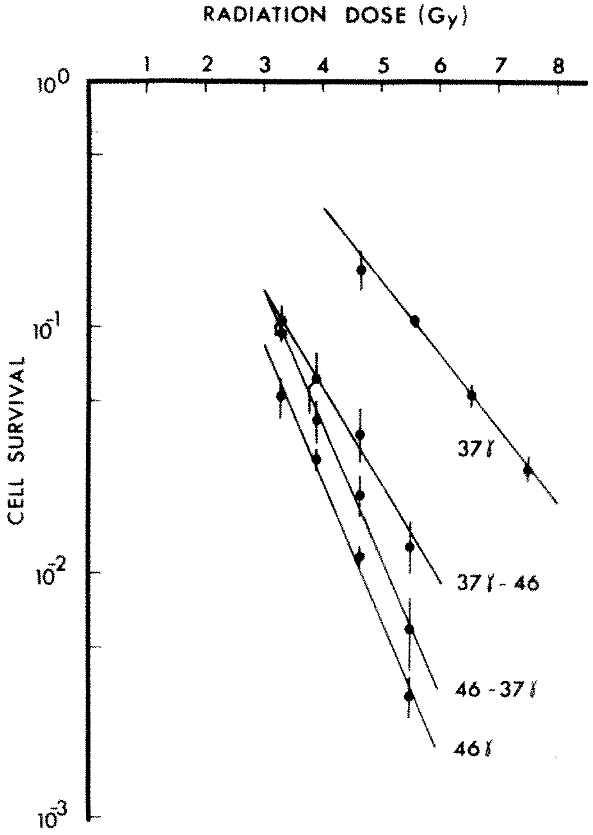


Fig. 2.

CHO cell radiation survival curves after the four treatment schedules described in the text. Data points show the mean and standard errors for four experiments (37γ–46 and 46 – 37γ) or eight experiments (46γ and 37γ).

Preliminary Illustrative Experiments

Sensitization of hyperthermia reponse by radiation

Asynchronous CHO cells in Hams F12 were plated in T30 flasks at concentrations of 10^3, 10^4 and 10^5 cells per flask. These flasks were heated to 37°C for 15 min and then to 44°C. Samples were withdrawn from the 44°C water bath at successive times. Five minutes after being cooled to room temperature half of the samples were given a total dose of 3.5 Gy of ^{60}Co γ radiation at a dose rate of 0.96 Gy/min.

The survival data for a single experiment are illustrated in Fig. 1. The survival curves exhibit shoulders followed by exponential parts which are steeper where the heating was followed by a radiation exposure, illustrating an interaction.

Sensitization of radiation response by hyperthermia

Asynchronous CHO cells cultured in Hams F10 were suspended in plain glass tubes at a concentration of 1.25×10^5 cells/ml. The tubes were heated from room temperature in water baths at 37°C or 46°C and irradiated through the sides of the water baths by a ^{60}Co teletherapy unit. The tubes occupied a selection from six positions in which the dose rates ranged from 1.5 Gy/min to 0.6 Gy/min.

Four treatment schedules were used: (a) irradiation at 37°C (37γ); (b) irradiation at 46°C (46γ) (c) irradiation at 37°C followed 3 min later by 7 min heat exposure at 46°C (37γ–46); (d) heat exposure at 46°C followed 3 min later by irradiation at 37°C (46–37γ). Exposure at 37°C or 46°C was for 7 min, irradiation starting 1.75 min after the heating started and stopping 0.25 min before heating was terminated by cooling in room temperature water. The temperature rise was exponential from room temperature with a half time of 30 s so exposure at 46°C resulted in a temperature above 42.5°C at the start of irradiation and a final temperature of 46°C.

In each experiment all of the tubes heated to 46°C were heated simultaneously, thereby providing exactly the same hyperthermia dose. Those tubes not irradiated (*e.g.* hyperthermia controls and tubes to be irradiated at 37°C), were positioned out of the radiation beam and received total doses of less than 0.01 Gy.

The survival data are illustrated in Fig. 2. Simultaneous heating at 46°C and irradiation increased the slope compared to the control irradiations at 37°C. Irradiation at 37°C 3 min after heating at 46°C increased the slope to a comparable extent and apparently increased the extrapolation number. Heating at 46°C 3 min after irradiation at 37°C resulted in an intermediate slope and reduced extrapolation number. Several aspects of interaction are illustrated by these data.

The design of the particular matrix experiment described in this paper is similar to procedure (d) 46–37γ, above. Although relaxation effects are outside the scope of this paper and are complex when radiation and hyperthermia interact, the experiment above suggests that the survival parameters for this particular experimental configuration are reasonably stable. An apparent increase in extrapolation number has been observed elsewhere (Henle and Leeper, 1976), but the useful application of the matrix type of experiment and appropriate analysis do not depend on particular changes of survival parameters. An increase in extrapolation number may be partly an artefact of radiation doses which are not completely off the shoulder of the survival curves and, while worthy of investigation, will not be discussed in this paper. However, the particular analysis used may be influenced by the apparent behaviour of the extrapolation number.

THE SURVIVAL SURFACE

Assume for the purpose of illustration that there might be no interaction between hyperthermia and radiation. An iso-survival plot as shown in Fig. 3 could be constructed. The contours on this plot represent equal survival levels each separated by a factor of 2, so that these contours represent survivals of $\frac{1}{2}$, $\frac{1}{4}$, $\frac{1}{8}$ and so on. In order to reduce the survival to $\frac{1}{8}$ a radiation dose of 4.5 Gy might be given or a hyperthermia dose of 125 min at 42°C. Alternatively, 3.5 Gy and 60 min at 42°C might be given. That is, any combination of radiation dose along this contour would yield a survival of $\frac{1}{8}$.

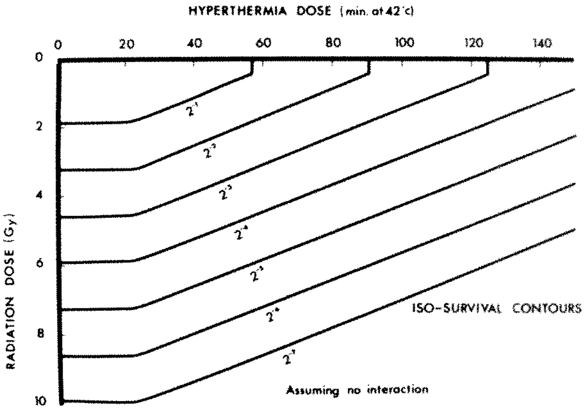


Fig. 3.

Hypothetical iso-survival plot constructed for the purpose of illustration on the assumption that there is no interaction between the effects of radiation and hyperthermia.

This type of plot is similar to a relief map. Just as the separation of the contours on a relief map indicates the relative steepness of the terrain, so the separation of the contours on this plot indicates the relative steepness of the survival surface.

Along the hyperthermia axis, after a region of low sensitivity indicated by the wide spacing of the contours, the contours become closer and evenly spaced, indicating a steeper slope that is exponential. For increasing hyperthermia dose, since the lines are parallel, the slope of the survival surface in the direction of increasing radiation effect remains unchanged. That is, in accordance with an assumption of no interaction, hyperthermia would not increase the slope of the radiation survival curve and conversely radiation would not affect the slope of the hyperthermia survival curve. It is evident, therefore, that if the interaction exists, the iso-survival contours cannot be straight parallel lines but must curve.

The three-dimensional survival surface corresponding to Fig. 3 exists in a space defined by radiation dose, D, hyperthermia dose, t, and the logarithm of the survival, $-lnS$, as three mutually orthogonal axes. It will be locally planar if there are regions where the iso-survival contours are straight parallel lines. If, however, the contours curve as suggested, the surface will not be planar.

Since the surface is expected to be smooth and continuous (*i.e.* there are no abrupt changes in survival or dose response for an infinitesimal change of t or D), the partial derivatives $\frac{\partial}{\partial t}\left(\frac{\partial lnS}{\partial D}\right)$ and $\frac{\partial}{\partial D}\left(\frac{\partial lnS}{\partial t}\right)$ will be defined and continuous over a region away from $D=O$ and $t=O$. These are sufficient criteria for the partial derivatives being equal. That is

$$\frac{\partial}{\partial t}\left(\frac{\partial lnS}{\partial D}\right)=\frac{\partial}{\partial D}\left(\frac{\partial lnS}{\partial t}\right)$$

Simply stated, this means that where for increasing hyperthermia doses the radiation survival curve is increasingly sensitized, then the hyperthermia survival curve must be increasingly sensitized for increasing radiation dose.

The intersection of the response surface with the $t=O$ plane is the unperturbed radiation survival curve in the more usual two-dimensional representation. Similarly, the intersection with the $D=O$ plane is the unperturbed hyperthermia survival curve. Sensitized or perturbed survival curves are obtained from the intersection of the survival surface with planes that are parallel to the $t=O$ plane or the $D=O$ plane. In any one plane only one value of sensitization is observed. However, the sensitization is a continuous function of dose which is explicit in the mathematical description of the full survival surface. A complete description of the surface will provide a complete description, though not an explanation, of the interaction.

In the model presented below, the detailed shape and curvature of the shoulders of the survival curves are ignored. Since the main analyses of this and the following paper (Loshek *et al.*, 1977) deal with the slopes of the survival curves, these curves are approximated mathematically in the form of ice-hockey sticks held upside-down, with a flat initial portion followed by an exponential region.

FIRST ORDER INTERACTION MODEL

The preliminary experimental examples above agree with a considerable body of published results to show that, at least over a limited range of doses and after a shoulder region, both the perturbed and unperturbed radiation survival curves are approximately exponential. To this approximation, the slopes of the radiation survival curves are dependent on hyperthermia dose, but independent of radiation dose. This yields the differential equation

$$\frac{\partial lnS}{\partial D}=f(t)$$

Similarly, over at least a limited range of hyperthermia doses, the perturbed and unperturbed survival curves are approximately exponential. To this approximation, the slopes of the hyperthermia survival curves are dependent on radiation dose, but independent of hyperthermia dose, yielding

$$\frac{\partial lnS}{\partial t}=f(D)$$

Integration of both differentials yields two general solutions with a particular solution satisfying both equations. Specifically this is

$$-lnS=C_1D+C_2t+C_3Dt+C_4,$$

and a distribution of the constant C_4 among the other three terms yields

$$-lnS=D_1K_R+t_1K_H+D_2t_2K_I \;\ldots\ldots\ldots\ldots (1)$$

$$\begin{array}{lll} \text{where } D_1 & =D-D_q & \text{for } D>D_q \\ & =O & \text{for } D\leqslant D_q \\ t_1 & =t-t_q & \text{for } t>t_q \\ & =O & \text{for } t\leqslant t_q \\ D_2 & =D-D_q{}^I & \text{for } D>D_q{}^I \\ & =O & \text{for } D\leqslant D_q{}^I \\ t_2 & =t-t_q{}^I & \text{for } t>t_q{}^I \\ & =O & \text{for } t\leqslant t_q{}^I \end{array}$$

If $t=O$ then both t_1 and t_2 are also zero giving

$$-lnS=(D-D_q)K_R$$

where $D-D_q=O$ for $D\leqslant D_q$. This is an ice-hockey stick approximation to the unperturbed radiation survival curve where K_R and D_q are the radiosensitivity and the quasi-threshold radiation dose for the control population. D_q is the radiation dose at which the exponential part of the curve intersects the dose axis. $K_R{}'$ with the dash will be used subsequently to denote the radiosensitivity of perturbed radiation survival curves where interaction increases the slopes.

Similarly K_H and t_q are the thermal-sensitivity and quasi-threshold hyperthermia time (hyperthermia dose) for the control population. $K_H{}'$ will be used subsequently to denote the slopes of perturbed hyperthermia survival curves and includes an interaction component.

$D_q{}^I$ is the radiation dose at which an extrapolation of the exponential part of a radiation survival curve perturbed by a hyperthermia dose intersects an extrapolation of the exponential part of the unperturbed curve when both have $lnS=O$ for zero radiation dose. Similarly $t_q{}^I$ is the hyperthermia dose for intersection. These doses are therefore the doses which require to be accumulated before interaction type events are evident. $D_q{}^I$ and $t_q{}^I$ will therefore be described as the interaction quasi-threshold radiation dose and the interaction quasi-threshold hyperthermia dose respectively. The parameters of equation 1 will be referred to as surface parameters, since the equation fits a surface to the data.

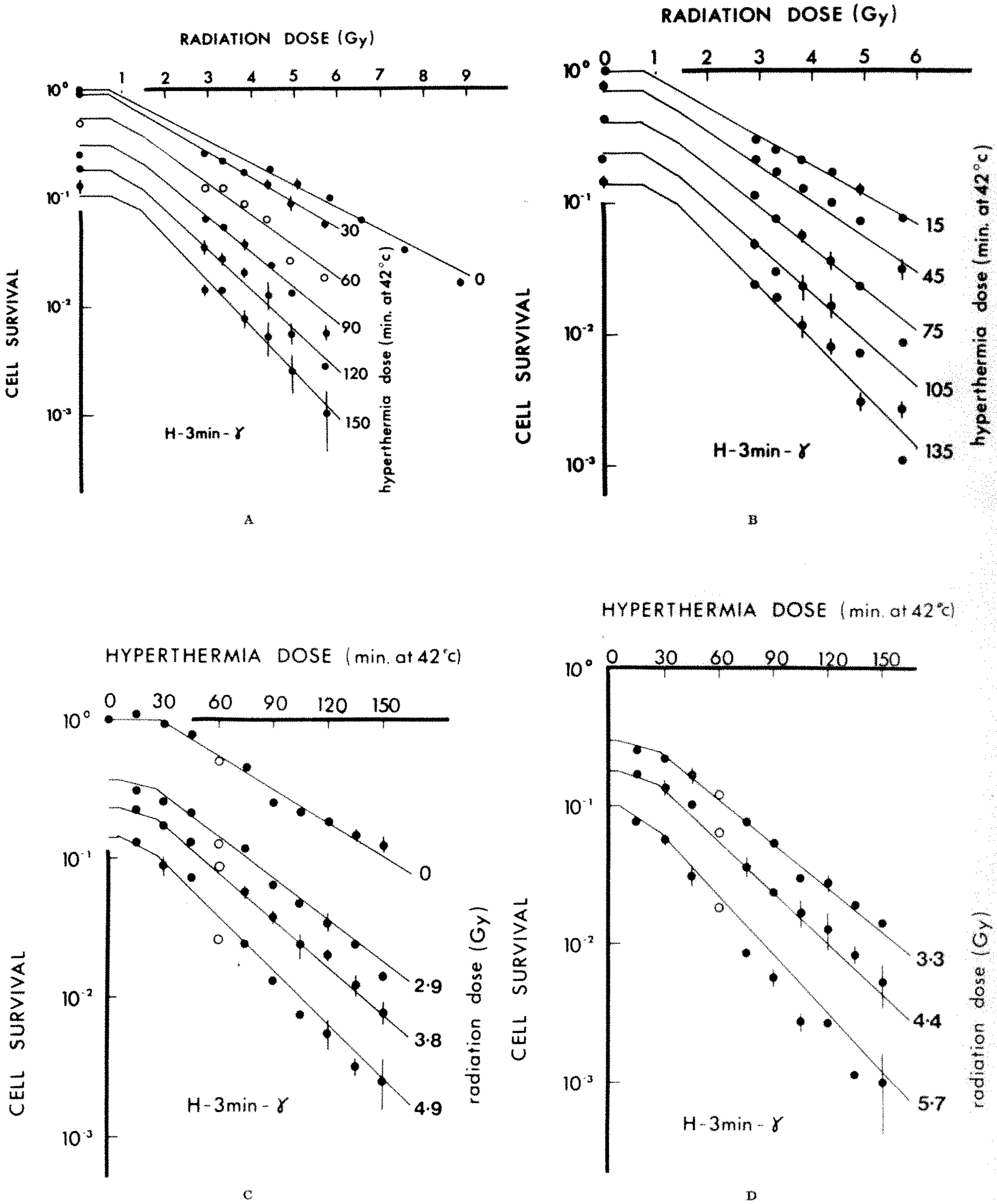


Fig. 4.

CHO cell survival for hyperthermia exposures followed 3 min later by ^{60}CO γ radiation doses at room temperature. The data points show the mean and standard errors from two experiments except for the open circles which represent a single observation. (A) and (B) show the survival data for the 77 combinations of radiation and hyperthermia doses plotted as radiation survival curves. (C) and (D) show the same data plotted as hyperthermia survival curves. The continuous lines are from equation 1.

THE MATRIX EXPERIMENT

The matrix experiment was designed to reduce the effects of experimental instability and to maximize the amount of information obtained. To obtain consistent survival data, it was desirable to collect the data for as many experimental points as possible within the context of a single experiment. To maximize the information obtainable without interpolation, each experiment was designed to yield survivals for a rectangular matrix of radiation and hyperthermia doses so that each row of the matrix would yield a radiation survival curve and each column would yield a hyperthermia survival curve.

In the matrix experiment described here no cell manipulation was required between heating and irradiation. A three-minute interval was therefore possible. Other versions of the matrix experiments have been carried out for other purposes. For example, where the analysis depended largely on the hyperthermia survival curves and cell manipulation was carried out between the treatments (Loshek *et al.*, 1977), the radiation was given first and an interval of 100 min was used. Although different amounts of relaxation occur with different orders and intervals, conditions can be found where parameters are relatively stable.

Experimental procedure

After trypsinizing, CHO cells in Hepes-buffered Hams F12 were plated into T30 flasks at three concentrations and flasks at each concentration were allotted to radiation and hyperthermia doses which were expected to produce a maximum of 500 clones per flask. Immediately after plating, the flasks were incubated at 37°C for 2 h and then cooled to room temperature. At this time cellular attachment to the plastic surface was virtually complete.

To ensure that all flasks received the same start to their hyperthermia treatment all the flasks to be heated were immersed in the waterbaths simultaneously. The flasks were mounted in a rack and immersed in a 37°C waterbath for 15 min, having been at room temperature for 30 min. The rack containing the flasks, heated to 37°C, was then quickly transferred to a waterbath maintained at 42°C.

At 15 min intervals flasks were removed, 15 flasks at a time. These were cooled in room temperature water for 1 min to terminate the heat exposure. Three minutes after removing each set of 15 flasks, 12 flasks were irradiated simultaneously, two at each of six different dose rates ranging from 2.8 to 1.4 Gy/min, leaving three flasks for the unirradiated controls. This procedure of a simultaneous irradiation at variable dose rates was regarded as being more satisfactory than sequential irradiation at a constant dose rate. Twenty-four unheated flasks were irradiated at the same six dose rates but to higher total doses. All flasks were maintained at room temperature during and for 1 h after irradiation or heating, before being incubated at 37°C. After six days the flasks were stained and counted.

This technique provided survival data for 77 combinations of radiation and hyperthermia doses, 11 radiation survival curves and seven hyperthermia survival curves.

Experimental results

Figures 4A and B illustrate the observed survival data plotted as a function of radiation dose and labelled with the corresponding hyperthermia doses. Figures 4C and D show the same data plotted as a function of hyperthermia dose and labelled with the corresponding radiation dose. The continuous lines in Fig. 4 are the calculated survivals derived from

TABLE I

INTERACTION PARAMETERS H—3 MIN—γ

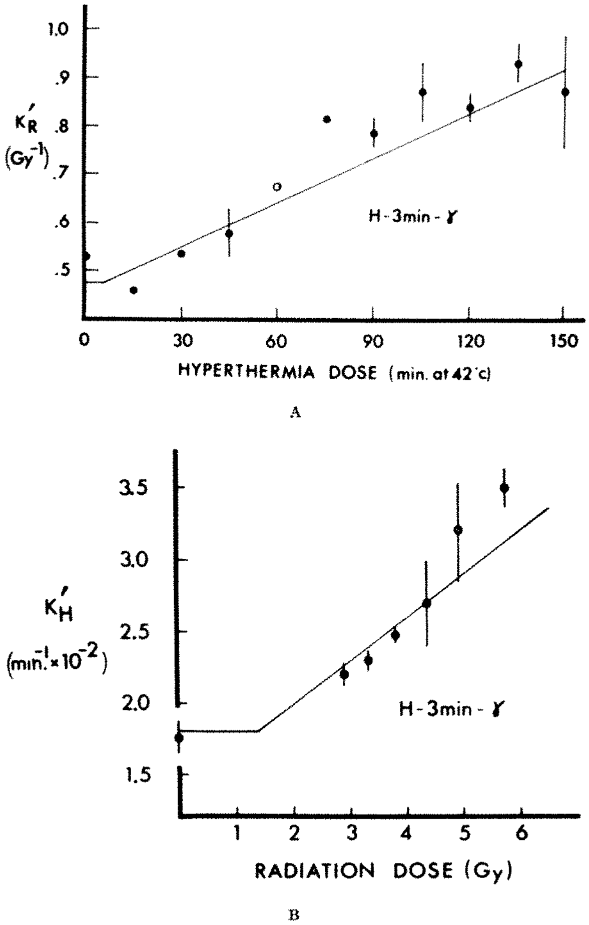
Parameter	Units	Multiplying factors	Surface	Unbiased
K_R	Gy^{-1}	10^{-1}	4.8	5.3 ± 0.0
D_q	Gy	10^{-1}	7.4	12.6 ± 0.4
K_H	min^{-1}	10^{-2}	1.8	1.8 ± 0.1
t_q	min	10	2.5	2.3 ± 0.6
D_q^I	Gy	1	1.4	2.1 ± 0.4
t_q^I	min	1	5.0	28.2 ± 8.5
K_I	$Gy^{-1}min^{-1}$	10^{-3}	3.4	4.1 ± 0.5
$\partial K_R'/\partial t$	$Gy^{-1}min^{-1}$	10^{-3}	..	3.6 ± 0.4
$\partial K_H'/\partial D$	$Gy^{-1}min^{-1}$	10^{-3}	..	4.7 ± 0.5

Note. Surface—parameters of equation 1; Unbiased—parameters of equations 4 and 5 (Appendix); Mean ± Standard Error.

equation 1 fitted to the experimental data points with the parameters given in Table I.

The data points in Fig. 5A illustrate the radiation survival curve slopes, K_R', derived separately for each hyperthermia dose using equation 2 in the Appendix. The dependence of K_R' on hyperthermia dose is shown by the slope of the data and is an estimate of the interaction coefficient (see Appendix). It should be noted that this figure shows that the value of the thermal enhancement ratio, T.E.R., is dependent on the magnitude of the hyperthermia dose.

A straight line through the values of K_R' intersects the level of K_R' corresponding to zero hyperthermia dose at the interaction quasi-threshold hyperthermia dose, $t_q{}^I$. The line in Fig. 5A is derived from equation 1 with the parameters of Table I.



A

B

FIG. 5.

(A) Radiation survival curve slopes, K_R', for each hyperthermia dose. (B) Hyperthermia survival curve slopes, K_H', for each radiation dose. The continuous lines are from equation 1.

The data points in Fig. 5B illustrate the hyperthermia survival curve slopes, K_H', derived separately for each radiation dose using equation 3 in the Appendix. The dependence of K_H' on radiation dose is shown by the slope of the data and is another estimate of K_I. A straight line through the values of K_H' intersects the level of K_H' corresponding to zero radiation dose at the interaction quasi-threshold radiation dose, $D_q{}^I$. The line in Fig. 5B is derived from equation 1 with the parameters of Table I.

Table I lists the parameters of equation 1 (surface) and the independent assessments of parameters obtained from equations 2 and 3 in the Appendix (unbiased).

The iso-survival contours for the experiment are shown in Fig. 6. These were obtained by solving equation 1 for the radiation dose required to obtain a given survival level for a series of hyperthermia doses. The iso-survival contours exhibit curvature.

DISCUSSION

Figures 4 and 5 show that the simple model of equation 1 does not provide an exact description of the experimental survival data. This is to be expected, as equation 1, formulated to describe survival on the exponential portions of the survival curves, has been applied to survivals near the shoulders.

The hyperthermia survival data exhibit a rather abrupt transition from the shoulder to the exponential portion. The radiation survival data, on the other hand, are still showing a tendency to increase in slope at the highest radiation doses. Equation 1, the surface fit, however, must fit a straight line to these

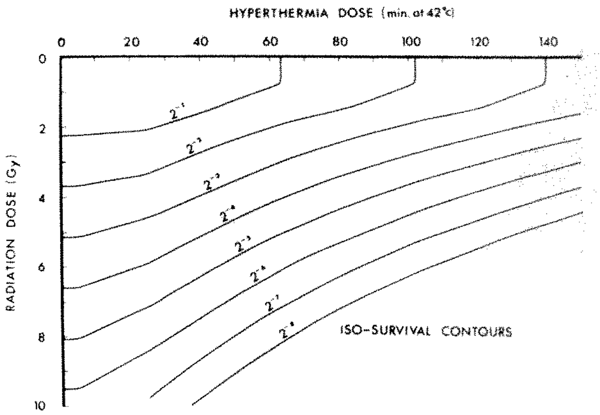


FIG. 6.

Actual iso-survival contours derived by equation 1 from the experimental data shown in Fig. 4. The curvature represents interaction.

slightly curving radiation survival data. Thus the highest radiation dose points of each radiation survival curve lie below the fitted line and therefore the lines fitted to the hyperthermia survival data corresponding to the two highest radiation doses lie above all the data points. It appears, therefore, that the increase in steepness of survival curves with sensitization, and the curve of the iso-survivals in Fig. 6, would be greater than shown if radiation survival had been followed to higher doses.

The mean of the interaction slopes, $(\partial K_R'/\partial t)$ and $(\partial K_H'/\partial D)$, determined as unbiased parameters, is within experimental error equal to the interaction coefficient K_I obtained from the surface fit of equation 1. The difference between the slope values may also be due to the slight curvature of the radiation survival data.

The radiation doses used for the unperturbed radiation survival curve were higher and more on the exponential part than those used for the perturbed curves. Consequently the radiosensitivity K_R of the former curve determined as an unbiased parameter from equation 2 in the Appendix is slightly higher than it would be if it were entirely consistent with the latter. This can be seen in Fig. 5A, and is the reason for the large difference between the surface and the unbiased values of $t_q{}^I$ in Table I, where 5.0 min corresponds to the surface fitted continuous line in Fig. 5A, and the value of 28.2 min corresponds to the level of the unbiased data point for zero hyperthermia dose. For the same reason, for the unperturbed radiation survival curve, the quasi-threshold dose D_q determined as an unbiased parameter from equation 2 is higher than when D_q is derived as part of the surface fit.

The model and the survival data are in partial agreement with the results of Robinson and Wizenberg (1974). They observed that the exposure of CHL cells to 42°C for variable times before, during and after irradiation resulted in a large jump in radiosensitivity for the first heating time of 15 min, followed by a less steep increase for heat exposures from 15 min to 120 min. If this behaviour is not the result of a peculiarity of the experimental conditions, the interaction observed must be of a biphasic nature.

The linear interaction observed here is of importance in analysing results presented in a paper (Ben-Hur *et al.*, 1974) which reported a large effect of radiation dose rate on the interaction of radiation and hyperthermia. It was reported that for low dose rates (0.033 Gy/min), the radiosensitivity of Chinese hamster cells irradiated at 42°C was 6.3 times greater than the radiosensitivity at 37°C, whereas for high dose rates (3.6 Gy/min), the radiosensitivity at 42°C was only 1.5 times as great as the radiosensitivity at 37°C. However, for the low dose rates, all of the cells were heated for five hours, while for the high dose rate the cells were heated only during their radiation exposure (*i.e.* the heating time was proportional to radiation dose and was a maximum of three minutes). While the low dose rate survival was indeed sensitized over four times as much as the high dose rate survival, those cells irradiated at the low dose rate had received 100 times the hyperthermia dose that the cells irradiated at the high dose rate had received. Thus it might seem that, contrary to the authors' suggestion, cells irradiated at a high dose rate are at least as susceptible to interaction as cells irradiated at a low dose rate.

CONCLUSION

The first order survival model has, as its virtue, a simplicity of expression rather than a great accuracy of prediction. However, as a good first approximation, the separation of the overall effects into three components, a purely radiation effect component, a purely hyperthermia effect component, and a first order interaction component, seems well supported.

K_R, K_H, D_q and t_q are familiar to most workers as the slopes and quasi-threshold doses of the unperturbed radiation and hyperthermia survival curves. The remaining parameters relating to the interaction, K_I, $D_q{}^I$ and $t_q{}^I$, are easily identifiable and conceptually similar to the parameters used to describe the unperturbed situation. Further, the physiological significance of the damage described by these interaction parameters can be given an experimental reality as shown in the subsequent paper.

More elaborate mathematical expressions might fit the data better, but unless the additional parameters can be given significance and meaning, elaboration would not contribute to a better understanding.

ACKNOWLEDGEMENT

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APPENDIX

DATA ANALYSIS

The data were analysed in two ways. In the first, giving the surface parameters, data for separate experiments were averaged and normalized to the survival at zero radiation dose and zero hyperthermia dose to obtain the survivals $S(t, D)$. The parameters of the survival surface described by equation 1 were obtained by a non-linear iterative technique.

In the second method of analysis, the radiation and the hyperthermia survival curve parameters were found for each curve and for each experiment. The radiation survivals for each hyperthermia dose were normalized to zero radiation dose for that hyperthermia dose and fitted by

$$-ln\frac{S(t,D)}{S(t,O)}=DK_R'-lnM_R' \text{ for } D \geqslant lnM_R'/K_R' \quad (2)$$

where K_R', the sensitivity, and M_R', the extrapolation number, are functions of t.

Similarly, hyperthermia survivals were fitted by

$$-ln\frac{S(t,D)}{S(O,D)}=tK_H'-lnM_H' \text{ for } t \geqslant lnM_H'/K_H' \quad (3)$$

where K_H' and M_H' are functions of D.

For both the radiation and the hyperthermia survival curves, all data points including those towards the shoulders of the survival curves were used to derive the parameters of equations (2) and (3). This approach eliminated bias which might have been introduced by the rejection of some of the data points, and the parameters are referred to as unbiased parameters.

Independent assessments of the interaction coefficient K_I were obtained by fitting the parameters K_R' and K_H' by the equations

$$K_R'=\left(\frac{\partial K_R'}{\partial t}\right)t + \text{constant} \quad . \quad . \quad . \quad (4)$$

$$K_H'=\left(\frac{\partial K_H'}{\partial D}\right)D + \text{constant} \quad . \quad . \quad (5)$$

The constants $\left(\frac{\partial K_R'}{\partial t}\right)$ and $\left(\frac{\partial K_H'}{\partial D}\right)$ are then separate estimates of the interaction coefficient. The values of K_R' and K_H' for $t=O$ and $D=O$ were not included.

The residual variance on K_R' and K_H', due mainly to inter-experiment variations in sensitivity, dominated the expected variance predicted by repeated Monte Carlo simulations of the matrix experiments. The dominance of the residual variance resulted in a variance that was approximately proportional to a constant percentage of the square of the value of K_R' or K_H'. Accordingly, the weights for K_R' and K_H' in equations 4 and 5 were taken to be

$$w_i=n_i/y_i^2$$

where y_i is the value of K_R' or K_H', n_i is the number of observations and w_i is the weight.

The best estimate of K_I was taken to be the weighted mean of $(\partial K_R'/\partial t)$ and $(\partial K_H'/ D)$, using the inverse variance of the parameters, $(\partial K_R'/\partial t)$ and $(\partial K_H'/\partial D)$, as weights. The error attached to K_I was the largest of the three: the standard error of the weighted mean, the standard error of $(\partial K_H'/\partial D)$, and the standard error of $(\partial K_R'/\partial t)$.

1977, *British Journal of Radiology*, *50*, 902–907

Interaction of hyperthermia and radiation: temperature coefficient of interaction

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ABSTRACT

Cell survival data were collected to determine the survival surface for asynchronous CHO cells X-irradiated at room temperature 100 min prior to a hyperthermic exposure. The survival surface could be approximately described by a survival model comprising three components of cell killing; the unperturbed radiation component, the unperturbed hyperthermia component and the interaction component. The temperature sensitivities of the hyperthermia component and of the interaction component were investigated by using different hyperthermic temperatures, revealing that the interaction component is significantly less sensitive to a change in temperature than the unperturbed hyperthermia component.

The possibility of using hyperthermia as a treatment modality of itself for the treatment of cancer or as an adjuvant to radiation therapy has prompted an investigation of the effects of temperature on thermal sensitivity. The effects of temperature on the unperturbed hyperthermia response of single cells have been well studied (Harris, 1967; Westra and Dewey, 1971). For mammalian cells the thermal sensitivity approximately doubles for every °C rise in temperature (Suit and Shwayder, 1974). Since equipment is being developed both to generate and measure the temperature of thermal fields within the body, this information is of vital importance in that it allows one to calculate the relative effects of a treatment across a non-uniformly heated volume.

If hyperthermia is used in combination with another treatment modality, the temperature sensitivity may change and will have to be assessed for each situation. The effect of temperature on the interaction between radiation and hyperthermia has been less studied (Robinson and Wizenberg, 1974; Robinson *et al.*, 1974). The use of an approach that allows separate assessments of the unperturbed hyperthermia component and of the interaction component of cell killing allows a more detailed analysis of the temperature sensitivity of the hyperthermia effect.

EXPERIMENTAL PROCEDURE

CHO cells were maintained in exponential growth in Hams F-12, supplemented with 15% calf serum, non-essential amino acids and glutamine. The pH of the medium was maintained at 7.2 with 20 mM Hepes buffer. Asynchronous cells were harvested by trypsinization and treated in suspension.

Since the main analysis depended on the hyperthermia inactivation rates as a function of radiation dose, it was desirable to have each hyperthermia survival curve as statistically reliable as possible. Therefore, a separate cell concentration was plated for each perturbed hyperthermia survival curve.

CHO cells were suspended at a concentration of 1.25×10^5 cells/ml in seven plastic T30 flasks. Allowing one flask for radiation control, the other six flasks were irradiated with graded doses of X rays at room temperature. The irradiations were sequential, the high dose flasks being irradiated first and the low dose flasks last. The six irradiations required a time interval of 15 min. This additional time is not included in the 100-min. interval mentioned below which is the time from the last irradiation to the start of heating. Studies of the decrease of interaction with increasing intervals separating radiation and hyperthermia doses, under somewhat different conditions, revealed that during the 100-min. interval necessary for the additional cell manipulation very little relaxation of the interaction occurred and that the change of interaction was very slow over the time interval required for the sequential irradiations. The irradiation conditions were: 250 kV, 15 mA, 1.8 mm Cu HVT, 1.35 Gy/min.

Each of the resulting seven populations was plated into a number of replicate T30 flasks at a concentration to yield 500 clones/flask if they were not further treated. One hundred minutes after the cells had been irradiated, heat treatment was started by immersing the flasks, except for the hyperthermia controls from each of the seven populations, in a waterbath at an elevated temperature. Samples from each population were removed simultaneously after an initial heating time sufficient to bring the survival to the edge of the shoulder of the curve and thereafter at seven equal time intervals chosen to give an acceptable minimum survival after the maximum heating. For example, at 42°C the time interval was 15 min. and at 45°C it was 2 min. These eight different heating times provided adequate data for determination of slope. After one hour at room temperature the flasks were incubated at 37°C for six days, stained and counted.

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Four flasks were allotted for each unheated survival point, three flasks for the heated but not irradiated survival points, and two flasks for each heated and irradiated survival point. The number of clones per flask decreased for increasing hyperthermia dose, expressed as time at the appropriate temperature. The resulting loss of statistical certainty about the observed survival was allowed for by using a least χ-square fit for the expected and observed total number of clones per point.

The experimental procedure described above yields a hyperthermia survival curve for each radiation dose and a radiation survival curve for each hyperthermia dose. The six radiation doses and the unirradiated population therefore give seven hyperthermia survival curves six of which are perturbed by radiation. The eight hyperthermia doses and the unheated population give nine radiation survival curves eight of which are perturbed by hyperthermia. The radiation survival curves and the hyperthermia survival curves are formed of either the rows or the columns of the total 63 data points if these are set out as a matrix.

The above matrix experiment was carried out a number of times (see Table I) at each of the nominal elevated temperatures, 42°C, 43°C, 44°C and 45°C.

RESULTS

The data were analysed as described previously (Loshek *et al.*, 1977), providing the hyperthermia inactivation rates, K'_{H}, as functions of radiation dose, D, and the radiosensitivities, K'_{R}, as functions of the hyperthermia dose, t. The slopes $(\partial K'_{\mathrm{R}}/\partial t)$ and $(\partial K'_{\mathrm{H}}/\partial D)$ of the sensitivity curves provide separate estimates of the interaction coefficient, K_{I}. These parameters are referred to in Table I as the unbiased parameters.

It was found that, for this particular experimental configuration, there was no correlation of extrapolation number with sensitizing dose. That is, the

TABLE I

INTERACTION PARAMETERS X-100MIN-H

Expt.	Parameter	Unit	Multiplying factor	Unbiased	Dose mod.	Surface
42°C (41.86°) 5 expts.	K_{R}	Gy^{-1}	10^{-1}	5.4 ± 0.3	5.4 ± 0.2	5.0 ± 0.2
	D_{q}	Gy	10^{-1}	5.6 ± 3.4	5.1 ± 0.8	4.6 ± 1.1
	K_{H}	min^{-1}	10^{-2}	2.2 ± 0.7	2.1 ± 0.2	2.2 ± 0.1
	t_{q}	min	10	2.2 ± 0.6	1.9 ± 0.2	2.1 ± 0.2
	K_{I}	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	4.6 ± 0.4	4.9 ± 0.4	4.6 ± 0.1
	$\partial K'_{\mathrm{R}}/\partial t$	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	4.3 ± 0.4	5.0 ± 0.3	
	$\partial K'_{\mathrm{H}}/\partial D$	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	5.0 ± 0.4	4.7 ± 0.4	
43°C (42.88°) 2 expts.	K_{R}	Gy^{-1}	10^{-1}	5.0 ± 0.0	5.5 ± 0.1	5.2 ± 0.1
	D_{q}	Gy	10^{-1}	5.7 ± 0.9	9.5 ± 2.2	7.5 ± 0.2
	K_{H}	min^{-1}	10^{-2}	6.1 ± 0.5	6.1 ± 0.4	6.4 ± 0.4
	t_{q}	min	10	3.0 ± 1.2	0.9 ± 0.3	1.1 ± 0.2
	K_{I}	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	9.3 ± 3.4	8.4 ± 1.1	6.9 ± 0.4
	$\partial K'_{\mathrm{R}}/\partial t$	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	5.9 ± 1.4	8.2 ± 0.9	
	$\partial K'_{\mathrm{H}}/\partial D$	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	12.5 ± 1.4	8.6 ± 1.1	
44°C (43.87°) 2 expts.	K_{R}	Gy^{-1}	10^{-1}	5.5 ± 0.2	5.6 ± 0.2	5.7 ± 0.1
	D_{q}	Gy	10^{-1}	4.7 ± 4.1	5.2 ± 4.2	4.8 ± 3.2
	K_{H}	min^{-1}	10^{-2}	15.6 ± 0.5	14.7 ± 0.7	14.9 ± 0.8
	t_{q}	min	10	1.0 ± 0.1	0.9 ± 0.2	0.9 ± 0.1
	K_{I}	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	12.3 ± 4.5	14.5 ± 1.6	12.2 ± 0.6
	$\partial K'_{\mathrm{R}}/\partial t$	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	17.6 ± 4.5	15.2 ± 1.6	
	$\partial K'_{\mathrm{H}}/\partial D$	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	10.6 ± 2.6*	14.2 ± 1.1	
45°C (44.77°) 3 expts.	K_{R}	Gy^{-1}	10^{-1}	6.1 ± 0.2	6.1 ± 0.3	5.8 ± 0.3
	D_{q}	Gy	10^{-1}	8.4 ± 1.9	8.2 ± 2.3	6.5 ± 1.7
	K_{H}	min^{-1}	10^{-2}	26.1 ± 7.7	25.8 ± 2.4	27.3 ± 3.1
	t_{q}	min	10	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.3
	K_{I}	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	22.2 ± 4.9	17.2 ± 1.9	16.1 ± 1.7
	$\partial K'_{\mathrm{R}}/\partial t$	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	21.9 ± 2.5	21.9 ± 1.9	
	$\partial K'_{\mathrm{H}}/\partial D$	$\mathrm{Gy}^{-1}\mathrm{min}^{-1}$	10^{-3}	23.0 ± 4.9	14.8 ± 1.4	

* $\partial K'_{\mathrm{H}}/\partial D$ (44°) unbiased parameter determination does not include 7.0 Gy point.
Mean ± Standard Error.

sensitization appeared to be dose-modifying. It was therefore regarded as justifiable to attribute a common radiation extrapolation number and a common hyperthermia extrapolation number to the survival curves for each row and column of the matrix. This is the same as assuming the interaction quasi-threshold doses to be zero. It should be noted that the results given in Loshek *et al.* (1977), with a somewhat different arrangement of the matrix experiment, showed correlations of extrapolation numbers with sensitizing dose, and non-zero interaction quasi-threshold doses.

Assuming common extrapolation numbers the parameters of the surface model (Loshek *et al.*, 1977) expressed in equation (1) below were obtained for each experiment separately.

$$-lnS = D_1K_R \times t_1K_H \times DtK_I \qquad (1)$$

where $D_1 = D - D_q$ for $D > D_q$

$= O$ for $D \leqslant D_q$

and $t_1 = t - t_q$ for $t > t_q$

$= O$ for $t \leqslant t_q$

Finally, as a third method of analysis, the parameters of equations (2) and (3) below were determined by a combined iterative search for the best common extrapolation numbers M'_R and M'_H and a linear least squares determination of the corresponding slopes K'_R and K'_H.

$$-lnS = DK'_R - lnM'_R \text{ for } D \geqslant lnM'_R/K'_R \qquad (2)$$

$$-lnS = tK'_H - lnM'_H \text{ for } t \geqslant lnM'_H/K'_H \qquad (3)$$

The slopes $(\partial K'_R/\partial t)$ and $(\partial K'_H/\partial D)$ of the sensitivity curves were obtained as described earlier, but include the zero dose points in the fit, unlike those for the unbiased fits. These parameters are referred to as dose modifying parameters.

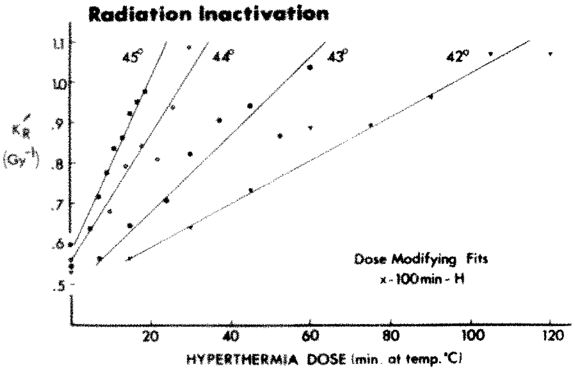


Fig. 1.

Radiosensitivity, K'_R, to 250 kV X rays at room temperature followed 100 min later by a hyperthermia exposure at the indicated temperature and duration. K'_R was calculated assuming a common radiation extrapolation number for each experiment. Data points represent the mean of the number of experiments indicated in Table I. Standard errors are not indicated.

The parameters of the surface model, and for both the unbiased and dose modifying independent assessments of radiosensitivity, thermal sensitivity, and interaction, are listed in Table I.

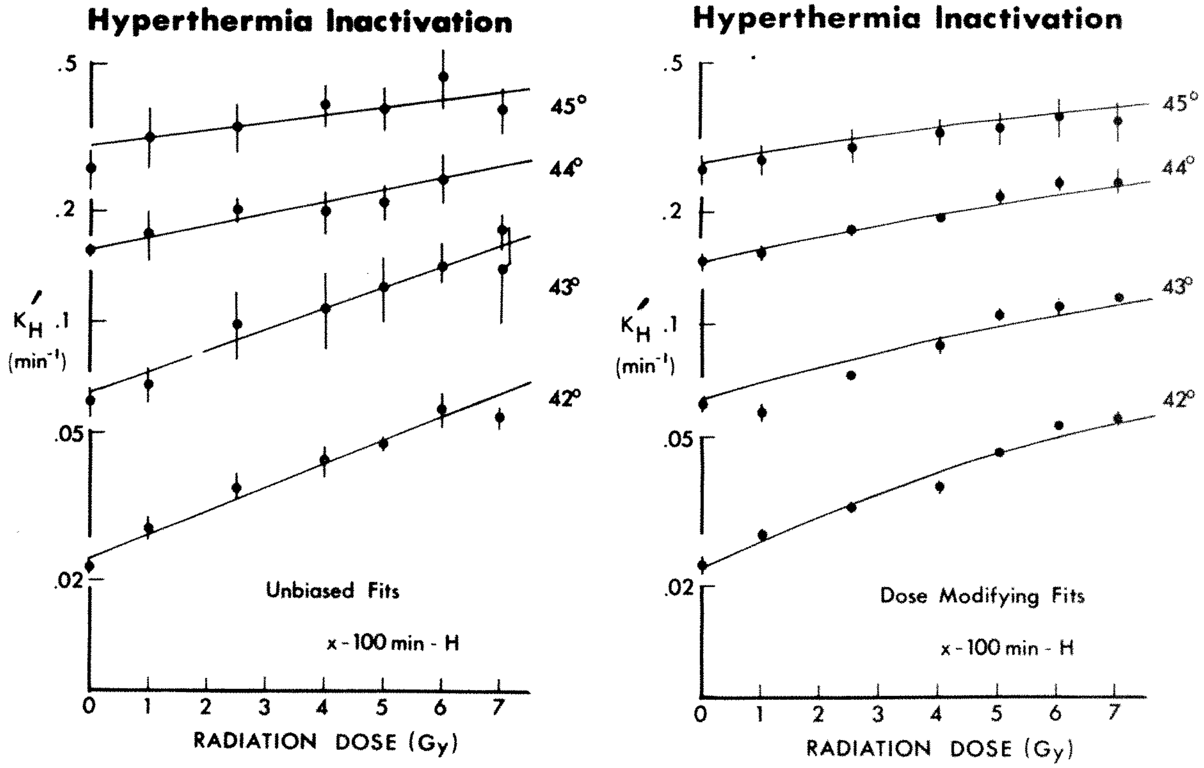
Figure 1 illustrates the values of the radiation survival curve slopes, calculated using a common extrapolation number within each experiment. It is observed, as anticipated, that as the temperature increases there is an increase in the sensitization of radiation response for a given heating time, as indicated by the divergence of the experimental points at different temperatures. Figures 2A and 2B illustrate the thermal inactivation rates at different temperatures, plotted as a function of radiation dose. As the radiation dose increases, the logarithms of the thermal sensitivities for different temperatures converge. This indicates that, as the temperature increases, there is a decrease in the factor by which a particular radiation dose sensitizes the hyperthermic response.

The hyperthermia inactivation rates for each radiation dose were used to calculate the activation enthalpies, illustrated in Fig. 3. It is assumed that there is an equivalence between the number of cells surviving and the amount of some chemical species remaining unreacted. A progressive reduction in activation enthalpy for increasing radiation dose is evident.

As the temperature increases, the increase in relative radiation sensitivity for a given hyperthermia exposure time and the decrease in relative hyperthermic sensitization for a given radiation dose are compatible with the increasing prominence of a component of cell killing which possesses a significantly smaller activation enthalpy than the hyperthermia killing component. That this can be considered to be the situation is illustrated by the Arrhenius plots of the unperturbed hyperthermia inactivation rates, K_H, and the interaction coefficients, K_I in Fig. 4.

Table II lists the activation enthalpies for the unperturbed hyperthermia inactivation rates, K_H, and the interaction coefficients, K_I, calculated from the three sets of parameters. It is observed that the calculated values of K_I for the three sets of parameters are significantly lower than the activation enthalpy for hyperthermic killing.

The control values of K_R obtained for the 45°C experiments exhibit an unexplained variation compared to the experiments at the other temperatures, although experiments at 44°C and 42°C were done before, between, and after experiments at 45°C. This



A FIG. 2. B

Thermal sensitivity, K'_H, 100 min after a dose of 250 kV X rays at room temperature. The data points represent the mean and standard error for the number of observations indicated in Table I.

(A) Unbiased fits. Lines are drawn by eye to show the trends of the data points.

(B) Common extrapolation number fits. Lines are the thermal-sensitivities calculated from equation (1) using the parameters in Table I.

TABLE II

ACTIVATION ENTHALPIES FOR THE TEMPERATURE DEPENDENT INTERACTION PARAMETERS

Parameter	Activation enthalpy (kJ/mole)		
	Surface	Dose mod.	Unbiased
K_H	660±60	650±70	650±70
K_I	380±50	320±70	450±70
$\partial K'_R/\partial t$		350±60	480±30
$\partial K'_H/\partial D$		330±60	370±190

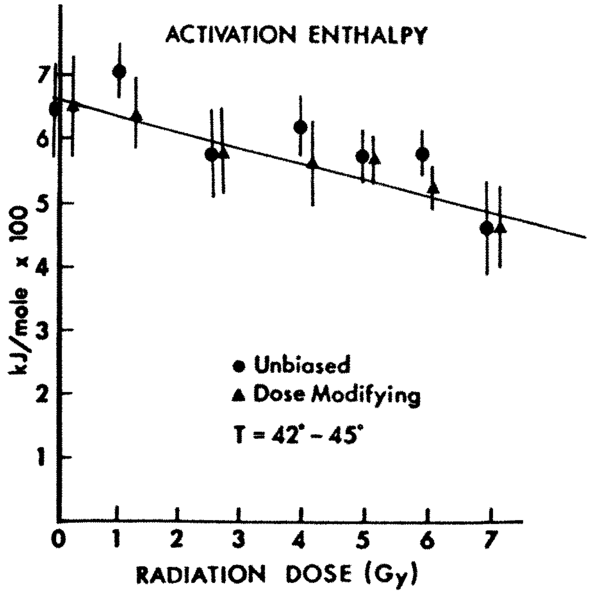


FIG. 3.

Activation enthalpy for hyperthermia inactivation 100 min. after a 250 kV X-ray dose at room temperature. Data points represent the mean and the standard error of fit.

variation has not been compensated for. The Arrhenius plots of the independent assessments of K_I do not all exhibit the same degree of linearity as that illustrated in Fig. 4. The activation enthalpies have, nevertheless, been computed and reflect only the average temperature sensitivity of the interaction.

Discussion

A comparison of the normal component parameters of hyperthermia, K_H, and radiation, K_R, obtained by the three analytical methods reveals only marginally significant variations. A comparison of the interaction coefficient, K_I, obtained by the three methods, however, reveals marked variations in a few of the estimates. Using the best common radiation and common hyperthermia extrapolation number for each experiment resulted in a reduction of the standard errors in three of the four data sets, as illustrated in Figs. 2A and B. Fitting common extrapolation numbers and utilizing the zero dose points in the independent assessment of K_I, which simulates the constraints of equation (1), resulted in better agreement between the values of $(\partial K'_R/\partial t)$, $(\partial K'_H/\partial D)$, and of K_I. These observations suggest that the technique was appropriate, although the principal observation, of reduced activation enthalpies for K_H for increasing radiation dose, does not depend on this technique.

While the three techniques do not yield precisely the same activation enthalpy for K_I, the differences between the values for K_I and K_H are significant for each technique. Similar observations have been made for viruses (Trujillo and Dugan, 1972) and yeast (Wood, 1954). One hypothesis which provides an explanation of these findings is that the mechanisms for unperturbed hyperthermic cell killing and cell killing by hyperthermic-radiation interaction are not the same. While the interactions found in this investigation have been associated with hyperthermia doses which result in cell killing when used alone, others (Ben-Hur *et al.*, 1972, 1974; Robinson and Wizenberg, 1974) have reported an interaction due to sublethal doses of hyperthermia. Field *et al.* (1976), investigating the kinetics of the damage induced by hyperthermia-radiation interaction *in vivo*, observed that the effect due to the interaction component presented at a later time that was more characteristic of radiation damage than hyperthermia damage. These observations suggest that the mechanisms of hyperthermic killing and interaction killing are not coupled, further supporting the above hypothesis.

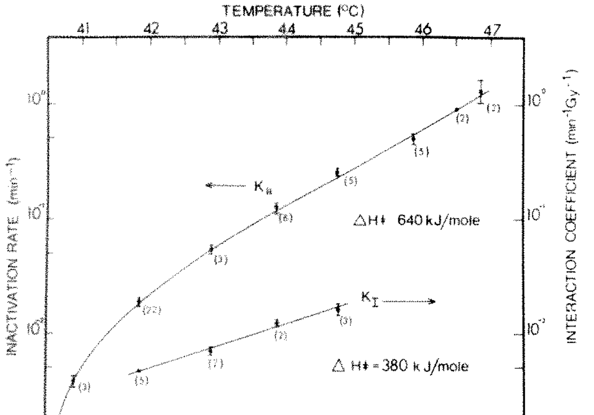


Fig. 4.

Arrhenius plot of the thermal sensitivity, K_H and the interaction coefficient K_I. The values for K_H include additional data derived from experiments within which only the thermal sensitivity was assayed. Error bars represent the standard error of the mean for the number of observations indicated in parentheses.

That a complex intermolecular organization is not required for the observations is well illustrated by the results of Sanner *et al.* (1972). They observed that a vegetable enzyme, pectin methyl esterase, was more heat labile after a radiation dose and that the degree of radiation effect on thermal sensitivity decreased for increasing temperature. The thermal sensitivity was characterized by an unperturbed activation enthalpy of 410 kJ/mole that decreased linearly with radiation dose to 290 kJ/mole, for a radiation dose that reduced the enzymatic activity to 40%. This behaviour, similar to that observed for CHO cells reported herein, occurs in a biological system in which a complex repair mechanism probably does not exist.

While the component of damage associated with the interaction between radiation and hyperthermia exhibits a lower activation enthalpy than the unperturbed hyperthermia component, the activation enthalpies for both components are sufficiently high to implicate physico-chemical reactions similar to those observed in the thermal denaturation of proteins. Thus it is suggested that the unperturbed component and the interaction component of the hyperthermia effect may act on different targets, although through reactions of a similar nature. Further, it seems possible that the interaction component of cell killing might arise from radiation and hyperthermia effects on a single target rather than separate effects on two complementary systems essential to cellular reproductive integrity.

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1977, *British Journal of Radiology*, 50, 908–912

Technical notes

A new technique of renography with electronically assisted kidney localization

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One of the greatest problems in clinical renography is the placing of the detectors. A correct detector position is mandatory in order to secure accurate determination of the fractional share of renal function to be ascribed to each of the two kidneys. We present a description of a new equipment designed to minimize the localization problem in clinical renography.

EXAMINATION PROCEDURE

During the last hour before renography, the patients were given orally approximately 750 ml of fluid. The patients were usually examined in the sitting position, with one detector unit pointing towards each kidney region and a third detector placed over the left scapular region for registration of the background radioactivity. After push-button selection of the analyzer window settings, 25 μCi ^{125}I–Hippuran was given intravenously. Placing of the detector units over the kidney regions at the positions of maximal count rate was performed by means of the localization system to be described. The analyzer settings were changed, and the renography proper was performed with ^{131}I–Hippuran, 0.2–0.4 μCi/kg.

DETECTOR UNITS

Figure 1 shows top, side and front views of a detector unit. The unit consists of four scintillation detectors with NaI (Tl) crystals, 3.2 cm diameter and 2.5 cm thick, mounted in a lead collimator so as to match the shape of the kidney. The distance from crystal to collimator opening is 4.8 cm. The detector unit is mounted in an easily adjustable stand.

The basic instrumentation comprises three linear ratemeters, a three-channel recorder and a tape recorder. During the recording of renograms after injection of ^{131}I–Hippuran, the count rates from the four separate detectors in each detector unit are added, and the integrated output is displayed on the linear ratemeter scales and in the recorder tracings.

ELECTRONIC SYSTEM FOR LOCALIZATION OF THE KIDNEYS

Figure 2 shows the detector unit and electronic system used for localization of the left kidney. The principle of localization in the vertical plane is as follows: after i.v. injection of ^{125}I–Hippuran, the added pulses from the two upper detectors (nos 3 and 4) are transmitted to one logarithmic ratemeter, and those from the two lower detectors (nos 1 and 2) to another. The ratio between the count rates in the two logarithmic ratemeters determines the position of the pointer on the instrument scale. Thus, the reading shows whether the detector unit is placed above, below or in the region of maximal radioactivity, *viz.* the kidney region proper. For example, if the detector unit is placed above the kidney, the count rate in detectors 1+2 is higher than that in detectors 3+4, and the pointer will indicate that the detector must be moved downwards. The horizontal position of the detector unit is checked in a similar way by means of a left/right display scale. The window setting for all analyzers of the system are identical and can be changed simultaneously by means of the push-button selection system.

INSTRUMENT PERFORMANCE

Investigations of the efficiency of the localization system and the characteristics of the collimator were carried out with a water-filled Perspex vessel with dimensions of the average human torso (Fig. 3). The kidney was represented by a Perspex phantom with a volume of 140 ml. The kidney phantom was filled with water containing 10 μCi ^{131}I–Hippuran.

Efficiency of the localization system

The kidney phantom was placed as shown in Fig. 3, so that a maximal count rate was recorded on the linear ratemeter scale; at the same time, the localization instrument pointer indicated a zero-setting, *i.e.* a minimal deviation from the centre line of the display scale. Thereafter, the detector unit was moved up, down, to the left and to the right, in 1 cm

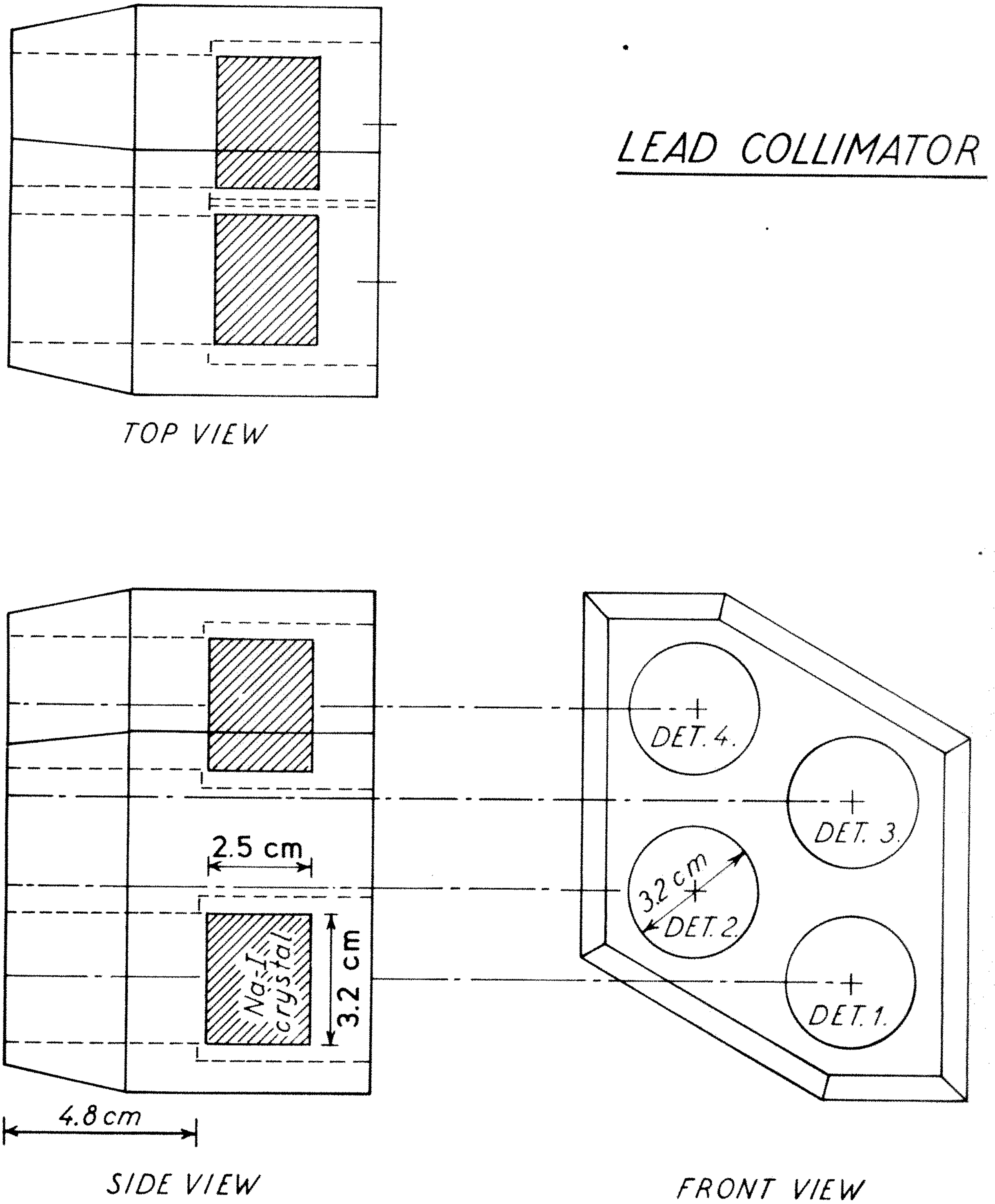

FIG. 1.
Top, side and front views of a detector unit.

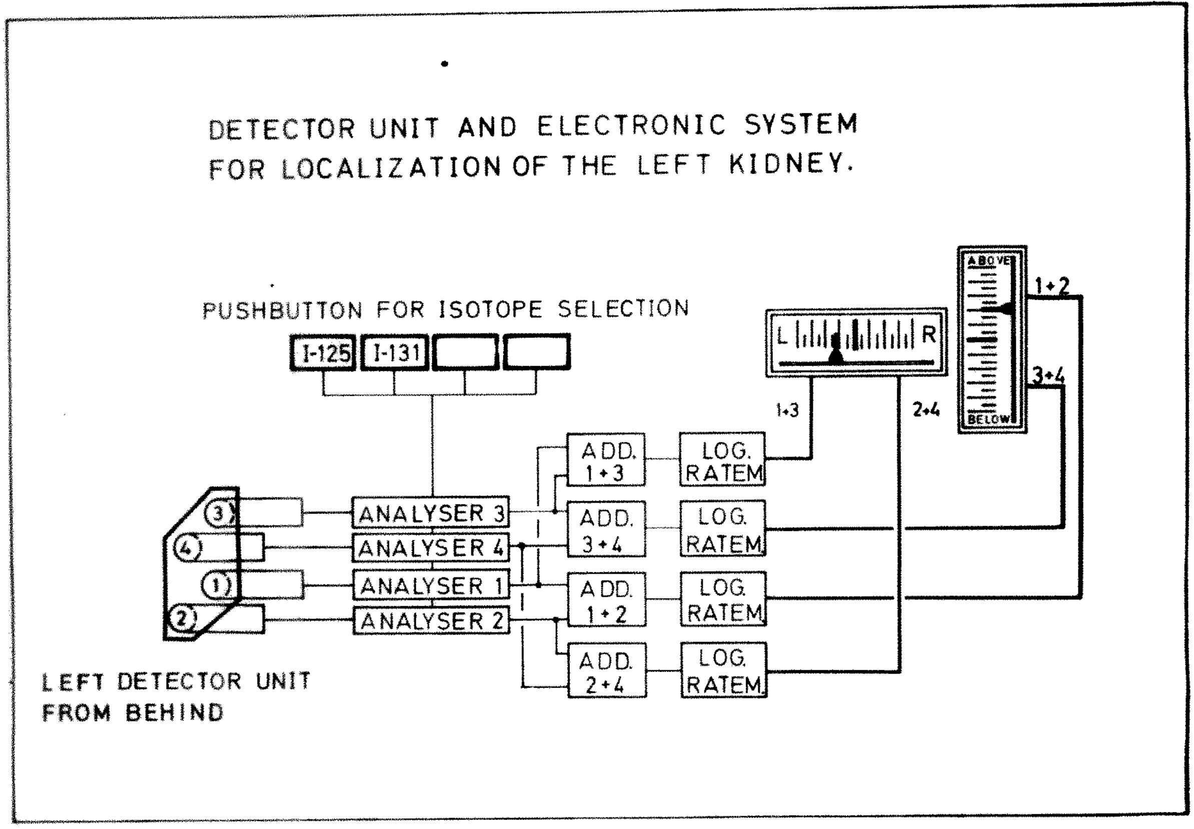

Fig. 2.

Detector unit and electronic system for localization of the left kidney.

steps. In each position the readings of the linear ratemeter and the localization instrument were noted.

Table I shows the results. When the detector unit was moved 1 cm up or down from the central position a 2% decrease in count rate was accompanied by a 20% deviation of the localization instrument. Movement of the detector unit 1 cm to the left or to the right resulted in a similar decrease in count rate, and a deviation of the localization instrument of 53%.

The cross radiation was measured with the detector units placed in five different ways: with the centre lines of the detector units parallel to each other and at angles of 15, 30, 60 and 90 deg. In each position the count rate was measured 11 times, the distance from the vessel wall to the centre of the kidney phantom varying from 3 to 13 cm. The per cent cross radiation was calculated from $100\,\frac{DR-B}{DL-B}$ where DR is the count rate from the right detector unit, DL that from the left one, and *B* the background count rate. Figure 4 shows the results. The cross radiation remained less than 3% up to a distance between vessel wall and kidney phantom of 10 cm and an angle between the centre lines of the detectors of 60 deg or less.

Isocount rate recordings were performed with a point source containing 10 μCi ^{131}I–Hippuran. The source was separated from the detector unit by a 4 cm thick paraffin sheet. In Fig. 5 the isocount rates are shown in per cent of the count rate from the source when placed in front of the centre of the detector unit.

Discussion

The equipment has been used routinely in our departments for three to four years in approximately 7000 examinations of patients with a variety of nephro-urological diseases (McNair *et al.*, 1976; Mogensen *et al.*, 1977; Munck *et al.*, 1975; Tønnesen *et al.*, 1975, 1976). The apparatus has

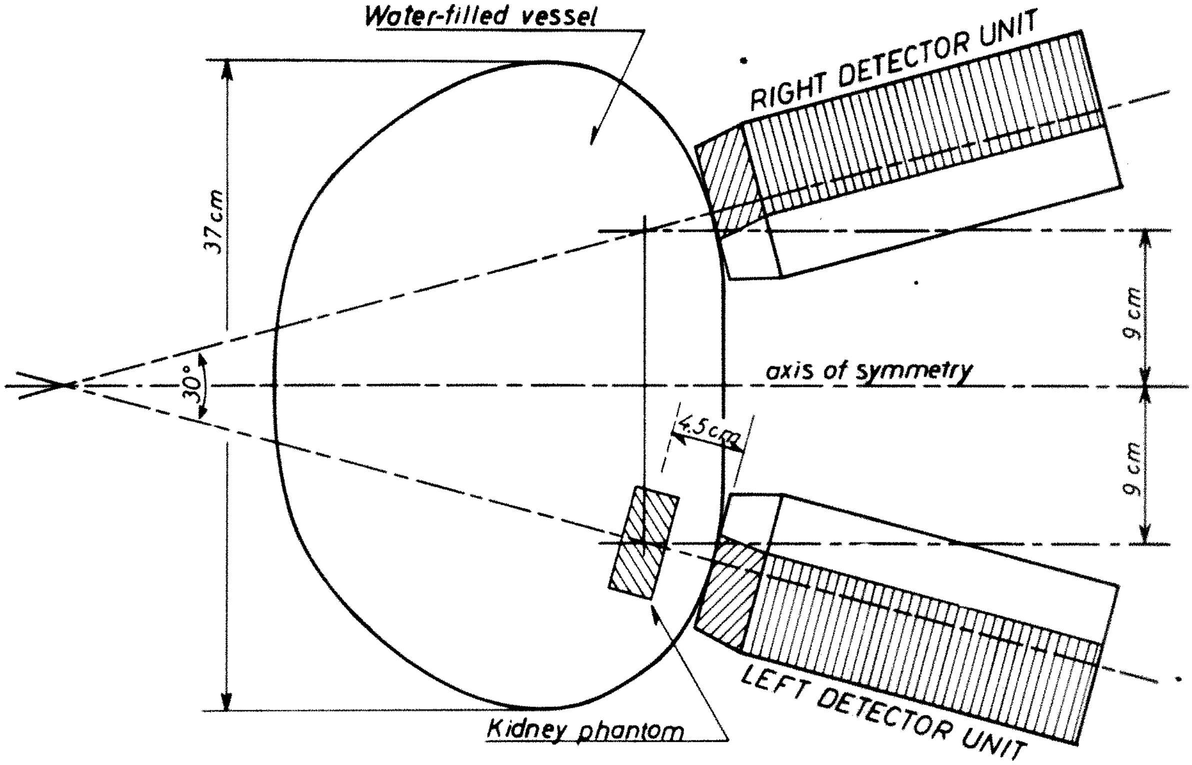

FIG. 3.
A schematic representation of the arrangement for testing the equipment.

TABLE I

EFFICIENCY OF THE LOCALIZATION SYSTEM TESTED WITH 10 μCi ^{131}I–HIPPURAN IN A 140 ML PERSPEX PHANTOM

Distance between the central axes of the phantom and the detector unit cm	Count rate per cent of maximum	Deviation of pointer on localization instrument per cent of maximum
Vertical plane		
zero	100	0
1	98	20
2	91	48
3	81	73
4	70	100
Horizontal plane		
zero	100	0
1	98	53
2	87	100

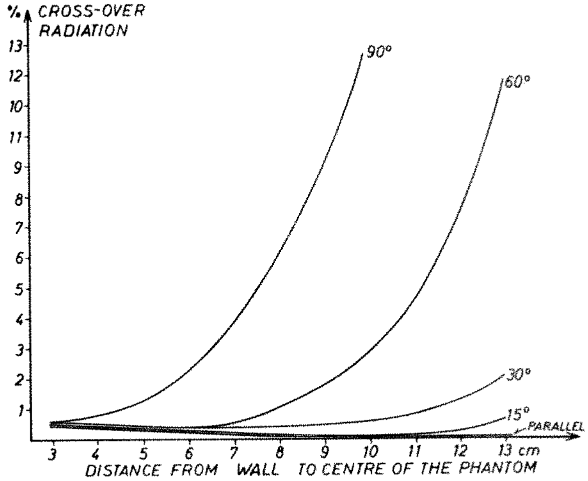

FIG. 4.
The correlation between the distance from the vessel wall to the centre of the kidney phantom (abscissa) and the cross radiation in per cent (ordinate) at different angles between the centre lines of the detector units.

1977, *British Journal of Radiology*, *50*, 912–915

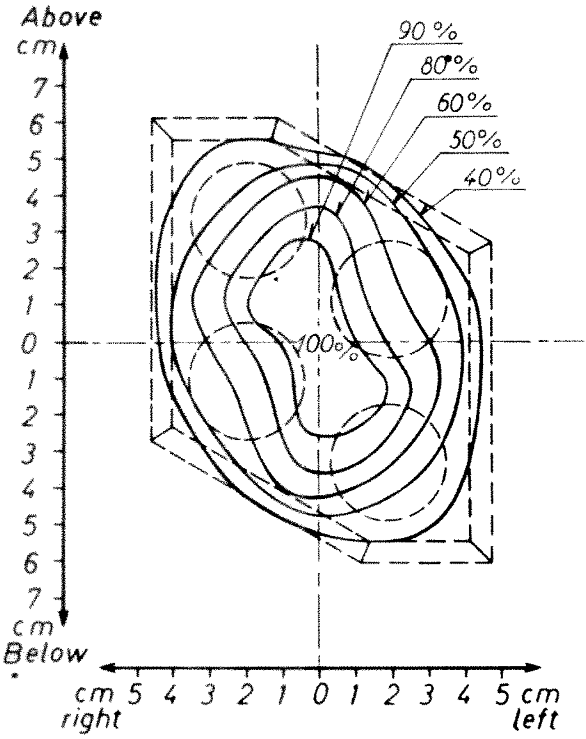

FIG. 5.

Isocount rate recordings for a detector unit obtained by use of a radioactive point source.

proved reliable and easy to handle. The equipment allows the renography procedure to be carried out by one nurse only, a point of considerable practical importance. The rather narrow field of view of the collimator minimizes cross radiation problems. The sensitive localization system provides the operator with a useful countermeasure against localization errors in clinical renography.

A localization renography system based upon these principles is commercially available from Mølsgaard Medical Aps, Gl. Strandvej 270, DK-3050 Humlebaek, Denmark.

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Design and fabrication of lead hexagonal multihole collimators

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For the dynamic study of cerebral circulation using technetium 99m, multihole collimators were required for two pairs of scintillation detectors. One pair was to be situated over the cerebral hemispheres to cover the region served by the middle cerebral arteries (Ring, 1969; Bell *et al.*, 1972.) Parallel hole collimators were considered satisfactory for this purpose. The other pair was to be placed over the carotid arteries; in this case well-shielded focusing collimators were required. For low energy γ rays like those of $^{99}\mathrm{Tc}^{\mathrm{m}}$, a honeycomb arrangement of hexagonal holes with thin-walled septa combines maximum sensitivity with good resolution; hence our designs were based on this concept from the outset.

FABRICATION

The traditional method of casting thin-walled lead collimators was not practical due to the formation of oxide layers, shrinkage and the requirement for expensive moulds. Wood's metal (Georgi, 1965) displayed minimal shrinkage and could be melted in

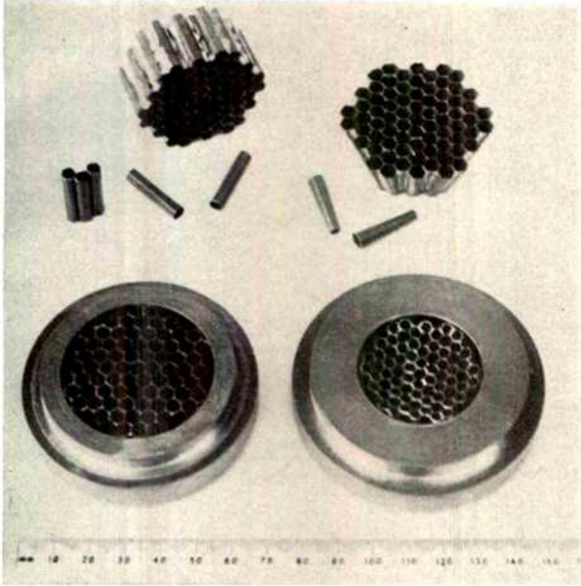

FIG. 1.

(A) Left middle: Straight hexagonal tubes used to make up array, shown on top left. Final collimator assembly shown on bottom left.

(B) Right middle: Tapered tubes used to make up array to form focused collimator, shown top right. Final assembly shown bottom right.

hot water but still required the use of moulds. These could be made with fine saw cuts in blocks of foamed Polystyrol but, owing to the small thickness required (0.25 mm), the septa would be non-uniform and air bubbles would be present.

Drilled collimators were also made for comparative studies and a septal thickness of 0.25 mm was achieved with the parallel-hole collimators. The focused collimators were drilled by inclining the drill at various angles, thus the septa were tapered and thick at the divergent end.

By using hexagonal holes, a 10% increase in sensitivity can be achieved (Mallard, 1972) due to the more uniform septal thickness and closer packing density. The final collimators were made of lead foil 0.25 mm thick, folded into hexagonal tubes which were then soldered together. Allen keys were used as formers for the parallel hole collimators but special brass formers had to be made for the tapered-hole collimators.

The parallel holes measured 4 mm across the flat sides and were 20 mm long. The lead foil was first cut into strips approximately 25 mm wide and then shaped around a 4 mm Allen key. A butt-joint was formed and lightly soldered to form a hexagonal tube as shown in Fig. 1. The hexagonal tubes were then soldered together to form hexagonal arrays

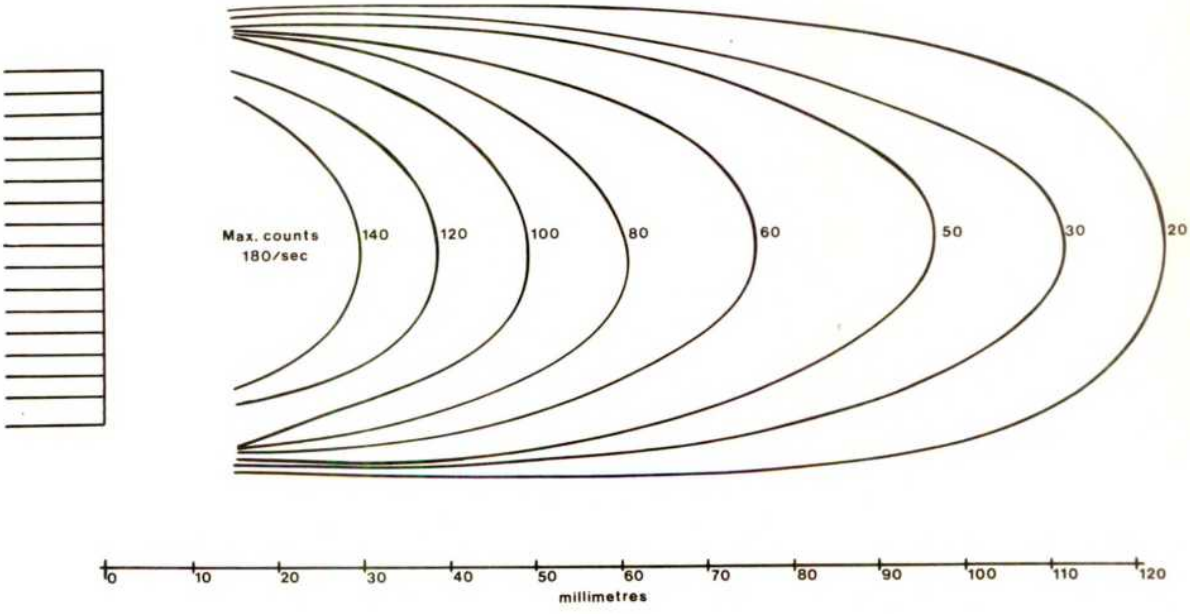

FIG. 2.

Isocount curves for parallel hole collimator. Curves were obtained by counting a point source of cobalt-57 mounted on a 2.5 mm pitch matrix board, fixed at the bottom of a Perspex tank filled with water.

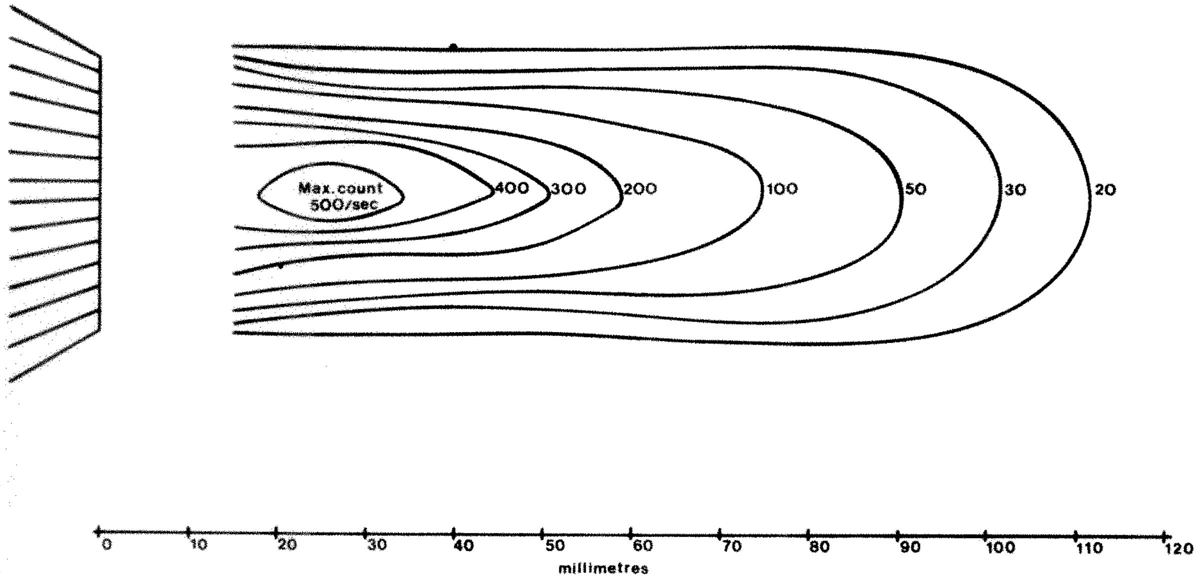

FIG. 3.
Isocount curves for focused collimator, obtained by the same method as in Fig. 2.

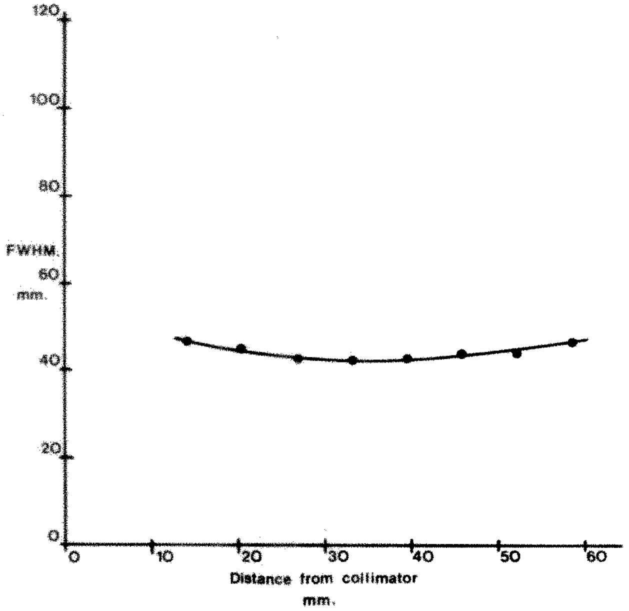

FIG. 4.
Variation of full width at half maximum along the central axis for paralled hole collimator, calculated from the curves of Fig. 2.

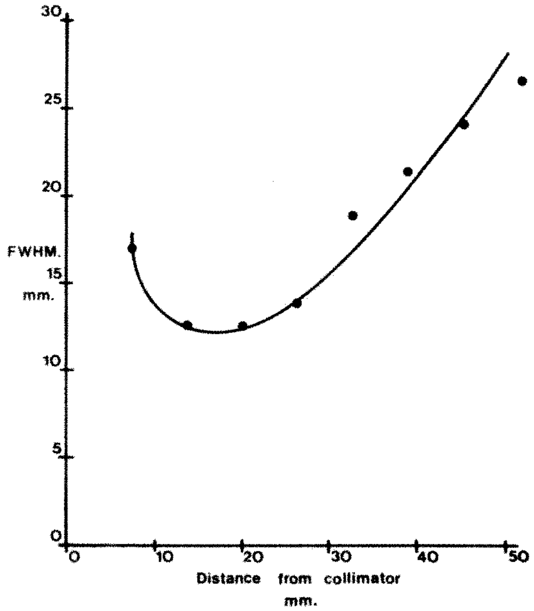

FIG. 5.
Variation of full width at half maximum along the central axis for focused collimator, obtained from curves of Fig. 3.

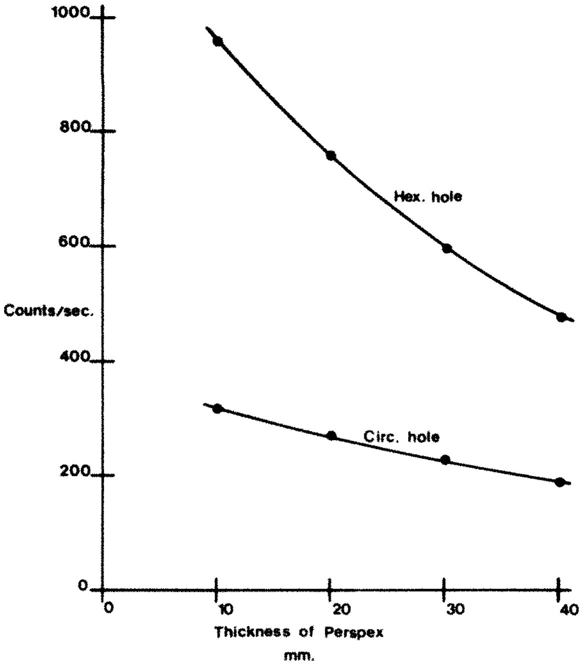

Fig. 6.

Comparison of sensitivities of the parallel hole hexagonal-tube collimator with circular hole collimator which was drilled from a block of lead. The source consisted of a sheet of blotting paper soaked with $^{99}Tc^{m}$ and mounted on sheets of Perspex of varying thickness.

until a collimator measuring 40 mm in diameter was made. The ends of the collimator were finished off to the correct length of 20 mm by embedding in dental wax and turning on a lathe. The collimator was then fixed to a mounting ring made from disused radioisotope generators.

Although it appeared to be a tedious and fiddly procedure, with some practice it was possible to make a 74-hole hexagonal array in only one day. The chief difficulty was to align the hexagonal tubes properly before applying the solder. This was done entirely by eye using a few Allen keys to hold the tubes in place. As the tubes were all hexagonal, they fitted together into a regular pattern and it was quite apparent to the naked eye whenever a tube was out of alignment.

The convergent collimators were made in exactly the same way except that a tapered brass former was used. A hexagonal brass rod was milled to give the exact degree of taper and this was used with the lead foil to fabricate two converging collimators, each with 74 holes, measuring 3 mm at the tapered end and 5 mm at the divergent end as shown in Fig. 1. The overall diameter was 50 mm at the divergent end and tapered to 35 mm. The length was 20 mm.

Results

The characteristics of both types of collimator were determined experimentally. A matrix board with holes at 2.5 mm separation was fixed to the bottom of a Perspex tank filled with water. The count rate due to a point source of cobalt 57 was established at different points on the board. In this way isocount curves were plotted and the results are shown in the figures.

Acknowledgments

Special thanks to Roland Dye and Dave Owst of the Regional Radiation Protection Service for the design and production of the detector shields, mountings and drilled collimators. Thanks are due as well to Ranjit Johal for typing the manuscript.

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Case reports

Localized giant pseudopolyposis of the colon in granulomatous colitis: a case report and review of the literature

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(*Received October, 1976*)

ABSTRACT

A case of localized giant pseudopolyposis of the colon is presented. The case was proven histologically to be granulomatous colitis. This unusual manifestation of granulomatous colitis may mimic a large bowel carcinoma or less frequently villous adenoma. This is the first proven reported case of granulomatous colitis presenting in this manner.

The radiological features of granulomatous colitis are similar to those seen in regional enteritis. They include contour defects, skip lesions, longitudinal and transverse ulceration, eccentric bowel wall involvement with pseudodiverticula, strictures and pseudopolypoid changes. Fistulae and sinuses may also be seen. Pseudopolyps of the colon may occur in ulcerative and granulomatous colitis occurring in 12 to 19% of cases of ulcerative colitis (DeDombal *et al.*, 1966; Jalan *et al.*, 1969), but are an unusual finding in granulomatous colitis (Bercovitz *et al.*, 1973). Pseudopolyps are the most frequent local sequel of ulcerative colitis.

Pseudopolyps may be localized or diffuse and are usually small, measuring less than 1.5 cm in height (Hinrichs and Goldman, 1968). The isolated occurrence of localized giant colonic pseudopolyps is a rare phenomenon seen in ulcerative colitis. This report deals with a case of granulomatous colitis with localized giant pseudopolyposis which mimicked a carcinoma both on radiologic and operative findings.

CASE REPORT

A 57-year-old male of Chinese origin was admitted to hospital with bright red blood being passed with bowel movements for ten days. Prior to this he had been aware of excessive peristalsis in the abdomen for three months. There were no associated abnormalities of bowel movements and there was no history of pain. Prior to this episode the patient had enjoyed good health.

Physical examination was non-contributory with no evidence of masses or tenderness. Bowel sounds were normal. The liver edge was just palpable below the right costal margin.

Laboratory investigations were within normal limits with a haemoglobin of 12·1 gm per 100 ml.

A barium enema demonstrated an irregularly narrowed segment in the region of the hepatic flexure measuring about 4 cm in length (Fig. 1). This was associated with irregularity and nodularity at its proximal end and there appeared to be overhanging borders at both its proximal and distal extents. The mucosal pattern in this segment was markedly distorted. The appearances were considered suggestive of a primary carcinoma involving the hepatic flexure.

At operation the lesion was considered in keeping with a bulky carcinoma of the hepatic flexure. The regional lymph nodes were normal as was the rest of the abdomen.

PATHOLOGICAL REPORT

A moderately well circumscribed lesion involving the caecum and the first part of the ascending colon measuring 6×6·5 cm was noted. The lesion involved the entire circumference of the wall and was composed of multiple various sized and shaped polyps with a smooth and congested surface. Some of the polyps were unusually long and measured 6 to 7·5 cm in length (Fig. 2). The long polyps were mostly at the periphery of the lesion and the smaller ones closer to the centre. The central part of the lesion measuring approximately 3×3 cm was firm and ulcerated. The lesion appeared to infiltrate the wall and underlying it there were some serosal adhesions.

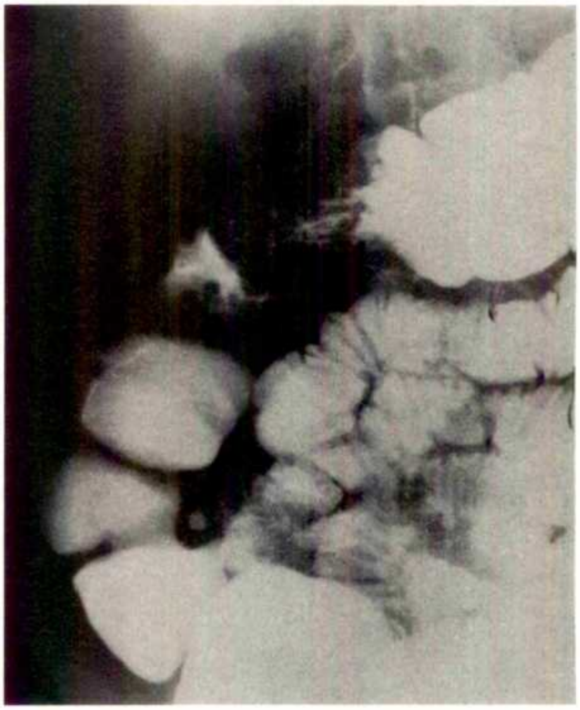

FIG. 1.

Supine view of the hepatic flexure showing a constricting lesion involving a segment over 5 cm long. An abnormality extends into the ascending colon where the linear filling defects represent large pseudopolyps. The resemblance to an annular constricting carcinoma is striking.

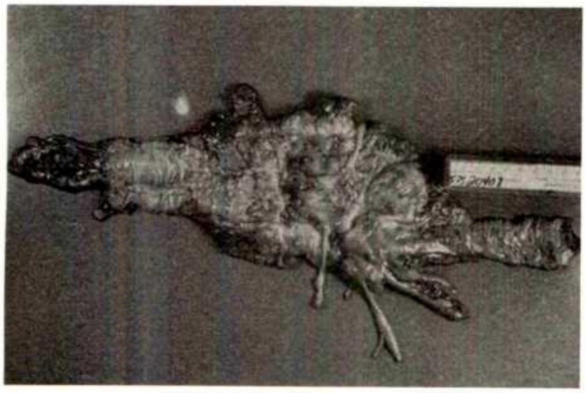

FIG. 2.

The resected surgical specimen showing a fairly well circumscribed lesion involving the entire circumference of the colon with multiple variously sized polyps. Some of the polyps measure 7.5 cm in length. The central part of the lesion is ulcerated.

Microscopic examination showed changes characteristic of Crohn's disease. The wall was markedly thickened and showed transmural inflammation with formation of non-caseating granulomata containing foreign body giant cells, prominence of nerve bundles and marked oedema in the submucosa. The lymphoid follicles were very prominent in the mucosa and submucosa. The lamina propria was densely infiltrated with inflammatory cells. Occasional crypt abscesses were seen. The polypoid lesions represented benign polypoid projections of the inflamed mucosa. Lymph nodes showed non-caseating granulomata with foreign body giant cell reaction.

DISCUSSION

To date only seven definite cases of giant polyposis have been reported (Hinrichs and Goldman, 1968; Bennett and Surridge, 1959; Finley and Begg, 1966; Ferrucci and Vickery, 1972; Goldgraber, 1965; Schneider *et al.*, 1973; Keating and Mindell, 1976). Only in the latter case was this described as a complication of granulomatous colitis, but the histology was not diagnostic, granulomata not being found. All other cases occurred in ulcerative colitis. In two cases (Finley and Begg, 1966; Ferrucci and Vickery, 1972) the described pseudopolypi were as large as was found in this case.

Most reports have emphasized that these lesions may mimic a carcinoma or villous adenoma (Schneider *et al.*, 1973). Villous adenoma can usually be distinguished by the fact that this tumour rarely involves the full circumference of the bowel and is usually lobulated and wart-like rather than villose. They also frequently coat poorly with barium due to their tendency to secrete excessive mucus. These lesions may sometimes be palpable on clinical examination (Keating and Mindell, 1976), and may cause partial obstruction to the retrograde flow of barium. The appearance of localized and unusually large polyps in a patient with ulcerative colitis frequently raises the suspicion of a carcinoma, but this appearance is in fact rare since the carcinoma that arises in ulcerative colitis is usually of the ulcerated or constrictive form (Morson, 1966). The occurrence of localized giant pseudopolyps of the colon is an uncommon event in ulcerative colitis and the presently described case is the first conclusive case to our knowledge of this phenomenon occurring in granulomatous colitis.

It appears that the possibility of inflammatory pseudopolyps should be considered in all patients with unexplained polypoid defects on barium enema, especially if there is supportive evidence elsewhere for inflammatory bowel disease. Most cases would still be subjected to laparotomy but it has been suggested that colonoscopy with biopsy may suffice (Schneider *et al.*, 1973).

ADDENDUM

A similar case of localized pseudopolyposis complicating granulomatous ileocolitis has recently been reported. (Wills and Han, 1977).

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Vertebral aspergillosis with preservation of the disc

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(*Received June, 1977*)

Infections with aspergillus organisms have been reported with increasing frequency in the last three decades. aspergillus fumigatus is by far the most common pathogen, but other species, aspergillus nidulans, aspergillus niger and aspergillus flavus also have been implicated. When aspergillus involves the spine, there is usually destruction of the intervening vertebral discs, as in other types of infection (Grossman, 1975). We have recently seen a patient in whom the discs were spread. This case appears to be unique and for this reason it is thought to merit publication.

CASE HISTORY

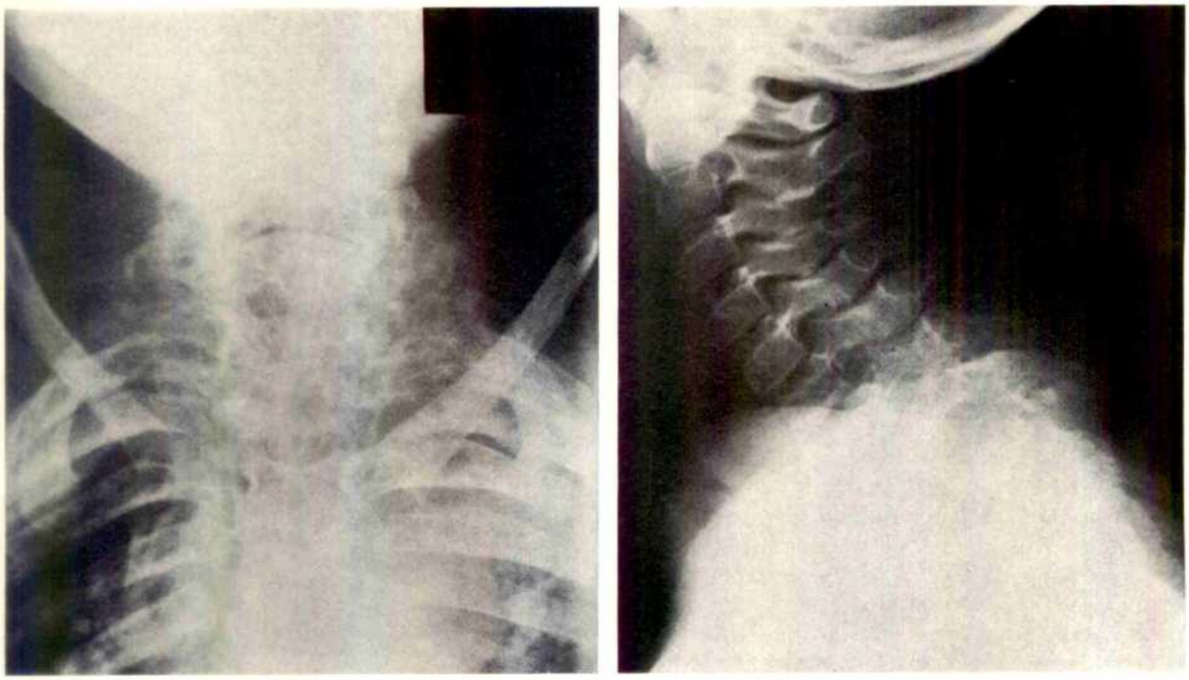
A nine-year-old white male (date of birth 3.10.1967) was admitted on 8.7.1974 with fever, cervical adenitis and a lung infection.

At the age of six months, he developed osteomyelitis of the frontal bone and septicaemia, and recovered on ampicillin. At 11 months he had severe enteritis and one month later he developed cervical adenitis with abscess formation which was drained from time to time and was treated with various antibiotics. Eventually a diagnosis of chronic granulomatous disease was made. In October 1973 he developed a swelling on the left side of his chest which was diagnosed as osteomyelitis of the seventh rib; this was resected and aspergillus fumigatus was found to be the causative organism.

In February 1974 he developed left upper lobe consolidation. At thoracotomy it was found that aspergillus involved not only the lungs but also the aorta.

In July 1974 there was abscess formation over the cervical vertebrae; this was incised twice and cultures later grew aspergillus. At this time destruction of the upper thoracic spine was seen on X rays (Fig. 1A and B).

Plain X rays and tomography of the cervical and dorsal spine showed partial collapse and destruction of the upper dorsal vertebrae. There was destruction of the tip of the spinous process of T1. Immediately below this area there was extensive soft tissue swelling. Slight forward slip of T1 on T2 was noted. Destruction of the corresponding ribs was present. The disc spaces were well preserved (Fig. 2).



A B

FIG. 1.

Lateral and A.P. view of cervical spine showing destruction of lower cervical and upper thoracic vertebrae.

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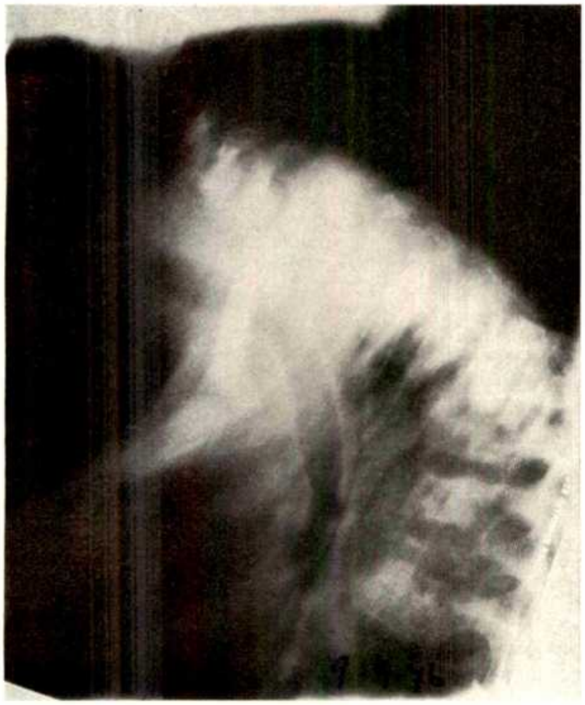

FIG. 2.

Lateral tomographic cut of thoracic spine. Note destruction of body of T5 with well preserved intravertebral disc spaces.

Involvement of the lower cervical and upper dorsal spine became progressively more extensive, but surprisingly the disc spaces remained intact. The appearance of the body of T7 was very much like that seen in eosinophilic granuloma. A chest X ray showed consolidation in the left upper lobe. The second, third, fourth and fifth ribs on the left side demonstrated irregular periosteal reaction (part of the seventh rib had been resected, Fig. 3).

In March 1975 a bone marrow transplant was performed; subsequently a small number of donor cells could be identified in the circulating blood. He improved somewhat but there was not a complete cure.

Discussion

The lung is a common site of aspergillosis, sometimes as a secondary complication of a pre-existing cavitating lung lesion. There are single or multiple areas of consolidation, often with cavitation. Involvement of other organs in the body has been reported: brain, liver, kidney, heart, thyroid, skin, testis, and also bone. Aspergillosis of bone is rare, and may result from direct spread of the primary lung lesion (Redmond *et al.*, 1965) or without a primary lesion in the lung (Shaw and Warthen, 1936; Green *et al.*, 1969).

It has been suggested (Finegold *et al.*, 1959) that antibiotic and cortisone therapy may be an important factor in establishing the fungus as a pathogen. Also it has been postulated, that the aspergillus gained entrance while the patient was receiving treatment for a salmonella infection during his first year of life (Redmond *et al.*, 1965).

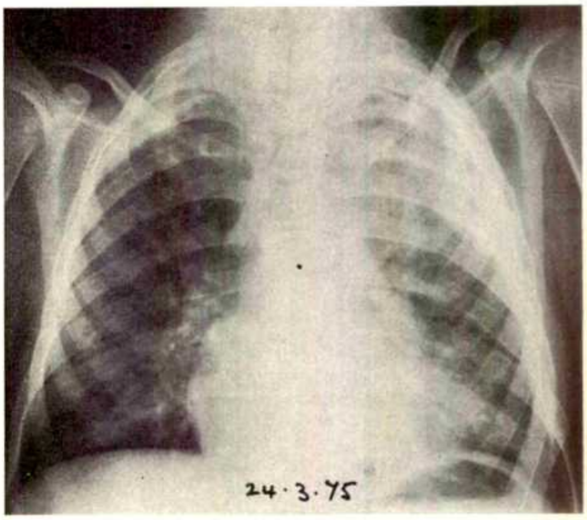

FIG. 3.

P.A. view of chest, showing consolidation in left upper lobe. There are extensive periosteal reactions involving the left upper ribs. Extrapleural effusion at right apex secondary to spinal lesion.

In patients with disorded immune response aspergillosis may become invasive. Grossman (1975) reported a case of aspergillosis of the spine from haematogenous dissemination of a primary lung lesion. The patient was on immunosuppresive therapy; a lung lesion was followed by destruction of two adjacent lumbar vertebral bodies with considerable narrowing of the related disc space. Periosteal reaction in the ribs and bones have been reported (Seres *et al.*, 1972) but no radiograph was included in his report. Periosteal rections in aspergillosis simulate other causes of rib infection, such as actinomycosis.

ACKNOWLEDGMENTS

I wish to thank Dr. K. Hugh-Jones, under whose care the patient was while at Westminster Children's Hospital and Dr. F. Starer, Consultant Radiologist of Westminster Children's Hospital, for his considerable help and encouragement in preparing this manuscript. I would also like to thank Westminster Hospital Medical Photographic Department for their assistance in the production of the illustrations.

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Obituary

E. Dale Trout, B.S., D.Sc.

The world of radiological physics and its offspring, health physics, will no longer be the same world without E. Dale Trout. Dale, as he was known the world over for decades, died on February 2, 1977 at the age of 75. He was almost the last of the small handful of scientifically-trained individuals who moved early into the little known fields of ionizing radiation and radiobiology.

E. Dale Trout, B.S., D.Sc., was born in Franklin, Indiana, on November 3, 1901 and graduated from Franklin College in 1922. From then until 1928 he taught high school science in nearby Illinois and thus had his first baptism of teaching, an area in which he has always excelled. It is probably that early teaching which helped him to develop a very keen sense of the need for simple and lucid explanations for basic principles. It certainly helped in his development of the pragmatic approach to many of the wide-ranging problems which he encountered in real life. It was also the start of one of his great dreams—to teach radiation physics in a University. The realization of this dream came when he retired from the General Electric X-ray Company in 1962 to become the Professor of Radiological Physics at Oregon State University. This was followed by his becoming Professor Emeritus at the University in Corvallis, Oregon, at which time he continued to carry a heavy teaching and research schedule in radiological subjects with special emphasis on the problems associated with the physics of diagnostic radiology.

To reach this dream, Dale had joined the Victor X-ray Corporation in Chicago in 1928 and stayed with that organization through its great expansion period, ultimately becoming the General Electric X-ray Corporation. Largely through his early connections with the Victor and G.E. companies, Dale travelled and spoke widely, not just in the United States, but the world over where he made and kept friends from just about every country that contained X-ray equipment, and probably some that did not. They called him a commercial engineer but he was not exactly one. He continued his work as a science teacher and radiation missionary and, in spite of being associated with a large commercial organization, his word was always accepted as conveying the best available information—and without commercial bias. Recognition of these attributes came through his being awarded an Honorary Degree of Doctor of Science from Franklin College in 1950.

It was my reward, for something, to have been able to know Dale Trout almost from his entry into the radiation field in 1928. From then our paths crossed frequently and we must have spent hundreds of hours together "talking shop". I have gleaned from him bits of information and treasure that he had derived from obscure sources, or from diligent library or personal research. An interesting example of this would have been his researches into the life and work of Christen in Switzerland—a name known early in the field of radiology but strangely overlooked in recent years. Dale even visited Christen's family in order to obtain or verify some information about his researches related to absorbed dose measurements and to descriptions of radiation quality by the half-value layer method.

In addition to his own work in industry or in teaching, Dale was always a willing helper in the voluminous voluntary committee activities which have marked our era. He has been a member of several of the scientific committees of the National Committee and now National Council on Radiation Protection and Measurements. He has been a member of Committee III of the International Commission on Radiological Protection. He has served on Committees of the International Electrotechnical Commission and the International Standards Organization. In the early 1950s Trout became an elected member of the NCRP and later a member of its Board of Directors, its Budget and Finance Committee and ultimately its Vice-President, a position which he was holding at the time of his death.

To those of us who were close to Dale, one of his charms was his humour—salty and clean and objective and homely. There seemed to be a story or an anecdote that would fit almost every situation, and Dale, in his modesty, attributed many of these to his "Grandpappy". A small tragedy for those of us still here is the fact that at the time of hearing these stories we never quickly wrote them down for posterity. Of the dozens that I have heard, I think of one in particular which occurred not too long ago as he was receiving a long overdue award from one of the professional organizations of which he was a member. Having listened to the extended speeches of presentation and acceptance preceding his, when his turn came he said "I am reminded of the man who had worked for many years in a parking lot and had finally received his driver's licence. Thank you."

There are many things about Trout which most of his friends knew relatively little about. For years, while in the Illinois area, he was an avid radio ham and must have had some of the finest amateur radio equipment in that part of the country—anything Dale made for himself had to be the best. To some extent he was a woodsman and for many years owned a large tract of woodland in British Columbia which furnished him a retreat from the pressures of the business world and even from his friends. Dale, having been raised on a farm, must have had some feeling for those who also struggled to realize their dreams. This feeling was vented very quietly and very privately, and probably not known to very many, by helping deserving young men to pay their way through college. I do not know how many of these there may have been, but the number was substantial.

Dale's achievement through his teaching, through his publications and through his industrial activities will surely be recounted. In the feeling of emptiness with which his loss leaves me, I have tried instead to touch upon some of those facets of his life which made him stand out in a way different from all others I have known. As I have said above, with Dale's loss radiological physics will no longer be the same. He is being missed by everyone who knew him.

In December of this year Dale was to have received the Gold Medal of the Radiological Society of North America—he would have been so proud of this. It will be awarded posthumously and received by his wife Thomesina. She will continue to live in their home in Corvallis, Oregon.

LAURISTON S. TAYLOR.

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DECEMBER 1977

Short communication

Effective measuring position for cylindrical ionization chambers when used for electron beam dosimetry

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When depth dose measurements are made for electron beams it is recommended that a flat chamber be used (ICRU 1972). Suitable chambers are now coming onto the market, *e.g.* that designed at the National Physical Laboratory (HPA 1975), but they are not yet universally available and are somewhat bulky for some applications. Therefore the cylindrical type of thimble chamber, hitherto the only type available, continues to be used.

When an ionization chamber is used to make central axis depth dose measurements in tissue-equivalent material, the exposure registered on the dosemeter is converted to electron dose in rads by applying a factor C_E which varies with energy and thus depth in the medium. Additionally a number of precautions and corrections must also be taken into account: namely saturation, polarity effects, stem and cable effects and perturbation and displacement corrections.

The displacement correction is necessary to determine the effective plane of measurement. For a flat chamber simple theory indicates that this is the front face, as the electron fluence is the same through the volume. The electrons traversing a thimble chamber of internal radius R with its axis at right angles to the electron beam will enter the measuring volume at distances up to R behind the front face, and simple calculation predicts that the effective measuring point will be $\frac{8R}{3\pi}$ (*i.e.* $0.85R$) in front of the axis of the chamber.

Because of scatter the radiation is not unidirectional. For a flat chamber the effective point of measurement has been shown by Dutreix and Dutreix (1966) to be displaced 10–20% of the depth towards its centre. This has been verified for the NPL flat chamber (Morris and Owen, 1975) by comparison with an extrapolation chamber. For the same reasons, the effective point of measurement in a thimble chamber is nearer to the axis than $0.85R$.

Measurements comparing flat and cylindrical chambers have been made by Hettinger *et al.* (1967) for electrons at 13 and 34 MeV. These indicate that $0.75R$ is the correct displacement correction and this is the figure which has been quoted in ICRU Report 21 (1972) and HPA Report Series No. 4 (1971).

Further measurements have been made by Dutreix and Dutreix (1966) at energies of 10 and 20 MeV; these indicate values of $0.65R$ at 10 MeV and between $0.65R$ and $0.85R$ at 20 MeV. However, corrections were not applied to the readings to account for the perturbation effect of the air volume in the chamber. This effect arises because more electrons are scattered into the cavity from the medium than are scattered back from the cavity and has been evaluated by Harder (1968). Since the perturbation correction is different for different chamber sizes and varies with energy, it affects the value found for the displacement correction. Morris and Owen (1975) concluded from calculations and from comparison with measurements using an extrapolation chamber that the perturbation correction for the NPL flat chamber was almost zero. They attributed this to the collecting volume of the chamber being defined by a guard ring and not by solid side walls. Corrections for cylindrical chambers, however, may rise to a few per cent; a table of values is given in ICRU Report 21 (1972). The net result is that values of ionization in cylindrical chambers need to be decreased relative to those in flat ionization chambers and to the dose measured by other methods.

Since the perturbation effect for cylindrical chambers increases with reduced energy or increased depth, on the steep part of the absorption curve the apparent displacement correction obtained relative to the flat chamber will be larger than that actually required when the values are reduced by the perturbation corrections. The corrections for effective measuring points given by both Hettinger *et al.* (1967) and Dutreix and Dutreix (1966) are thus too large (Fig. 1 should help to make this clear).

We have made central axis measurements in high impact polystyrene at energies from 3 MeV to 30 MeV with one cylindrical ionization chamber of internal diameter 3.5 mm and two others each with internal diameters of 6 mm; these measurements were compared with values obtained with the NPL flat chamber which has an effective diameter of 20 mm and a thickness of 2 mm, and requires a displacement correction of 0.2 mm from the front face (Morris and Owen, 1975).

Saturation was greater than 99% (Morris and Owen, 1975) and we could find no noticeable polarity effect up to 20 MeV; however, we did find a small polarity effect at higher energies both for this chamber and a 6 mm cylindrical chamber, although the correction was never more than 1% for either chamber. Stem and cable effects were also found to be negligible. To avoid systematic errors, we used the same absorbing material for all chambers as far as possible, and consider that positional errors were less than 0.1 mm.

Figure 2 shows the results obtained with the two larger cylindrical chambers and the flat chamber at 6 MeV, appropriate C_E factors and perturbation corrections having been applied to the data; the displacement correction is then

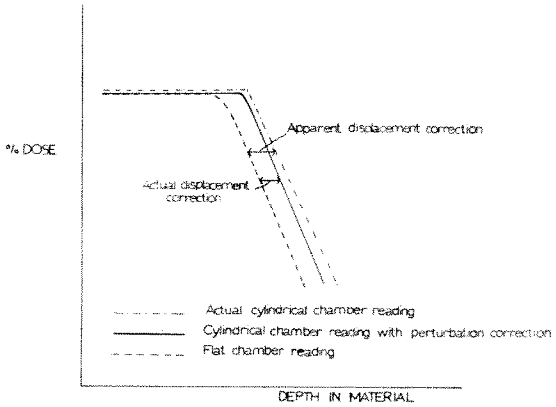
% DOSE
Apparent displacement correction
Actual displacement correction
Actual cylindrical chamber reading
Cylindrical chamber reading with perturbation correction
Flat chamber reading
DEPTH IN MATERIAL

FIG. 1.

Diagrammatic representation of the displacement corrections with and without perturbation corrections.

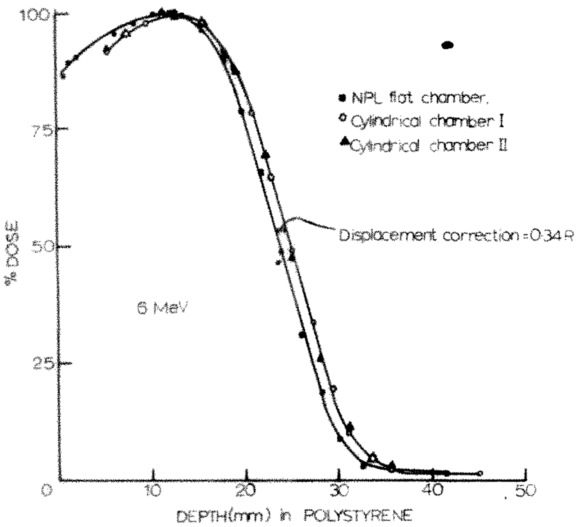

FIG. 2.

Depth dose curves for 6 MeV electrons plotted with flat and cylindrical chambers (C_E factors and perturbation corrections being applied)—displacement correction shown.

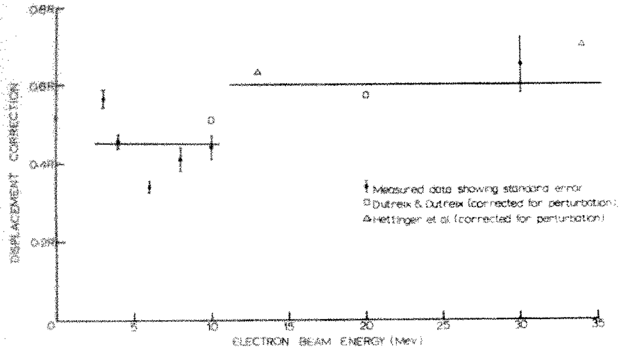

FIG. 3.

Variation of displacement correction with initial electron beam energy.

constant down the linear part of the curve. Measurement with the smaller chamber normally gave the same correction as the larger chamber to within less than 0.05*R*. Thermoluminescence measurements have also been undertaken using extruded lithium fluoride chips; these agreed with the flat chamber measurements within the limits of experimental accuracy.

The values obtained by all three cylindrical chambers are shown in Fig. 3, and are seen to fall substantially below the accepted value of 0.75*R*. This figure also includes the earlier data of Hettinger *et al.* (1967) and Dutreix and Dutreix (1966) corrected for the perturbation effect. These measurements together with our own at an energy of 30 MeV also indicate that a factor of 0.75*R* is too large. There appears to be some variation of the displacement correction with energy in the 3 to 35 MeV energy range and we believe it is not random. For practical application, we suggest that for a cylindrical chamber, radius *R*, the effective measuring position be considered as 0.45*R* in front of the centre in the 3 to 10 MeV energy range and 0.6*R* in the range above 10 MeV to 35MeV. Strictly the corrections apply only to the steep part of the curve but the correction makes a trivial difference to the rest of the depth dose curve. We suggest a constant correction be applied to the whole curve.

ACKNOWLEDGMENT

We wish to thank the Department of Radiotherapy, Bristol Royal Infirmary for the use of their betatron for measurements in the 12 to 30 MeV range.

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

A COMPARISON OF THE RBE OF FAST NEUTRONS AT EDINBURGH AND HAMMERSMITH

Radiotherapy with fast neutrons has recently begun at the Western General Hospital in Edinburgh. The neutrons are produced by bombarding a beryllium target with 15 MeV deuterons. At Hammersmith Hospital, London, where neutron therapy has been in progress for some years, the neutrons are similarly produced by 16 MeV deuterons. The biological effectiveness of the two beams is therefore expected to be similar and ultimately the results of therapy at these two centres will be compared.

In view of the importance of the project it was felt desirable to make experimental determinations of the relative biological effectiveness (RBE) of the two beams. Two tissue endpoints in mice were used for this purpose: (1) early skin reactions (Fowler *et al.*, 1965) and (2) survival of crypts in both jejunum and ileum (Withers and Elkind, 1970). For skin reactions neutron RBE has been shown to be similar in mouse and man at the same dose level (Field and Hornsey, 1971).

Irradiation was given in single doses and two fractions at 24 hours interval. On the same day mice were sent directly from their breeders to either Edinburgh or Hammersmith and after irradiation the Edinburgh animals were brought by train and finally by car to Hammersmith for scoring. To test that the journey from Edinburgh to London caused no differences in the biological response, both endpoints were also measured after single doses of X rays at the two centres. The dosimetry and irradiation procedures were strictly comparable at the two centres with both X rays and neutrons. The two beams of X rays were of the same energy, closely similar filtration and HVL.

All the experiments yielded consistent results except the gut irradiations at Hammersmith. In this single experiment a large number of mice died of an unknown cause and it was repeated using a new batch of mice, thus introducing a new variable.

Dose response curves were obtained for each type of treatment and from them the ratio of doses (R) at Edinburgh relative to those at Hammersmith to produce the same level of injury were estimated at several levels of damage. The mean values of R for the various treatments are given in Tables I and II.

The X-ray doses at the two centres to produce the same level of damage were sufficiently similar to indicate that the responses were unaffected by the journey from Edinburgh to London (Table I). It was therefore considered valid to compare the neutron results. It is seen in Table II that there were no significant differences observed in biological effectiveness of the fast neutron beams at Edinburgh and Hammersmith.

The experiment was made possible by the excellent help of many people, including Joan Beatty, D. Bonnett, J. Heather, Marilyn Law, M. Rogers, T. Saxton, Ann Silvester R. Tompkins and P. Warren.

Yours etc.,
S. B. FIELD,
CAROLINE C. MORRIS.

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TABLE I

MEAN VALUES OF RBE FOR X RAYS AT EDINBURGH COMPARED WITH X RAYS AT HAMMERSMITH (R_X)

Treatment	Endpoint	Range of dose per fraction (Gy)	R_X
Single doses	Skin reactions	20–40	1.00
Single doses	Crypt survival		
	(a) Jejunum	11–15	1.05
	(b) Ileum		1.05

TABLE II

MEAN VALUES OF RBE FOR FAST NEUTRONS AT EDINBURGH COMPARED WITH FAST NEUTRONS AT HAMMERSMITH (R_N)

Treatment	Endpoint	Range of dose per fraction (Gy)	R_N
Single doses	Skin reactions	14–20	1.05
Two fractions	Skin reactions	7.5–10.5	1.04
Single doses	Crypt survival		
	(a) Jejunum	5–8	0.98
	(b) Ileum		1.01
Two fractions	Crypt survival		
	(a) Jejunum	3–4.5	0.98
	(b) Ileum		0.93

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FIELD, S. B., and HORNSEY, S., 1971. RBE values for cyclotron neutrons for effects on normal tissues and tumours as a function of dose and dose fractionation. *European Journal of Cancer*, 7, 161–169.

FOWLER, J. F., KRAGT, K., ELLIS, R. E., LINDOP, P. J., and BERRY, R. J., 1965. The effect of divided doses of 15 MeV electrons on the skin of mice. *International Journal of Radiation Biology*, 9, 241–252.

WITHERS, H. R., and ELKIND, M. M., 1970. Microcolony survival assay for cells of mouse intestinal mucosa exposed to radiation. *International Journal of Radiation Biology*, 17, 261–267.

THE EDITOR—SIR,

A COST–BENEFIT COMPARATIVE ANALYSIS ON NEUTRON THERAPY VERSUS EXISTING RADIATION THERAPY TECHNIQUES IN SWITZERLAND

The alarming rate at which the cost of medicine is growing concerns the medical authorities of most countries more and more. One of many possibilities for fighting the inflation of medical costs is to give priority to new approaches which offer the greatest clinical benefits for the smallest cost. For this, an evaluation should be made of the cost, the benefit, and also the period of time necessary to make the programme efficient. It is desirable that such investigations be first carried out by people in the medical field before they are handed over to outside technocrats.

In as much as choices of radiotherapy are concerned, several approaches for improvement have been proposed, ranging from the very expensive π mesons to simply the improvement of already existing techniques. This present letter deals with costs and benefits from neutron therapy versus better use of classical equipment. Because of lack of accurate data, only estimates are made which, nevertheless, will probably be sufficient to support the discussion. The clinical benefit taken into account is the improvement in the five-year survival of the population of cancer patients treated by radiation over the country as a whole.

In a study of the various causes of failure in radiation therapy undertaken for supraglottic tumours treated at the Princess Margaret Hospital in Toronto (Niederer *et al.*, 1977), it has been shown that the improvement on the five-year survival rate of all stages would be about 8% (that is passing from 48% to 56%) if the technical failures (*i.e.* geographic miss, underdosage, etc.) could be eliminated. Another 8% improvement would be expected from a new treatment mode (*e.g.* neutrons) allowing complete control of the local and regional disease. Although these figures are valid for one particular tumour site treated at a large specialized hospital, it can reasonably be assumed that they might be applied, at least as a first approximation, to most other tumour sites treated by radiation.

Expected clinical benefit

Let us begin with the rather optimistic assumption that neutron beams may solve problems of radioresistance resulting, for example, from hypoxia, and that every cancer patient in the country would benefit from such a new technique. It is generally recognized that a neutron beam might be suitable only for some specific tumour sites, summarized in Table I, the incidence of which is of the order of 378 per million people, *i.e.* about 20% of all tumours treated by radiation. If we retain the value of 8% for the maximum increase in the survival rate when using this new technique, assuming there are no technical failures, then the benefit for the total cancer population treated by radiation could be approximately $0.2 \times 8 = 1.6\%$.

Technical failures influence the survival rate not only for the tumours listed in Table I, but also for Hodgkin's disease and for some other tumour sites (*e.g.* prostate, corpus uteri, ovary, testis and anal canal) which represent at least 30% of all tumours treated by radiation. A better control of the existing techniques, thus eliminating all technical failures, could allow an overall increase of the survival rate of 2.4% for the total population treated by radiation, based on the above mentioned value of 8% for the expected maximum increase in survival rate when technical failures are eliminated.

TABLE I

Mean number of patients of both sexes registered annually in Geneva (population 320000) during the period 1970–71 for tumour sites probably suitable for neutron therapy and corresponding annual incidence rate. (Source: Registre Genevois des Tumeurs)

Tumour site	Mean annual number of tumours registered in Geneva during the period 1970–71	Annual incidence rate per million people
Oropharynx	9	28.1
Rhinopharynx	1	3.1
Hypopharynx	5	15.6
Larynx	12	37.5
Cervix	37	115.0
Bladder	36	112.5
Astrocytoma grade III–IV	21	65.6
Total	121	378.0

Expected monetary cost

With a neutron therapy unit, an average of 20 patients could be irradiated per day, that is 5200 treatments a year. Assuming that approximately ten fractions are needed to complete a treatment, about 520 patients could be treated annually. About half the patients having tumours listed in Table I, *i.e.* 189 per million people, probably do not need to be treated with neutrons because they either have small tumours or distant metastases. Thus, a population of 520/189, *i.e.* nearly three million people, is needed to obtain the quota of 520 patients per year suitable for neutron therapy. The necessary investment would amount to approximately SF four million. This includes the purchase of the neutron therapy unit (SF three million), the construction or modification of the treatment room (SF 700000), the dosimetry equipment, the new computer programs, as well as the training of the medical and paramedical staff (SF300000).

For the optimal use of the existing techniques, what should the basic investment be to eliminate more or less completely all technical failures? In Switzerland and probably in most Western countries, the quantity and quality of the treatment units per million people, as well as the number of physicians, are already sufficient. However, as shown even in a hospital of such high quality as the PMH in Toronto (Niederer *et al.*, 1977), there has, even in recent years, been some room for improvement in the quality of the treatment. So, *a fortiori*, for the lesser experienced staff in smaller hospitals spread around the country. If we assume that one well-trained full-time team composed of one physician, two technicians, and one dosimetrist is enough for a population of 200000 people, 15 such teams would be needed for a population of three million people. If we accept that there are already at least five well trained teams, ten teams remain to be trained, at a cost of approximately SF200000 each. Thus, the maximum cost could be estimated to be of the order of SF two million.

A certain amount of money must still be spent annually to compensate for the turnover in the treatment teams and also for permanent training to keep up with new advances in radiation therapy. This is true for both approaches, but in the conservative approach 15 teams are involved opposed to one or two for neutron therapy. Let us also optimistically assume that a complete treatment with neutrons would be of similar cost to one with X rays when both types of machine are used in an optimal way. To be so, one neutron therapy unit should cover the needs of a population of three million people. There is no place in Switzerland where the density of population is such that all people who otherwise could be treated as out-patients could still be so treated. Thus, part of the 520 patients treated per year would have to be lodged somewhere and would receive an allowance for transportation and for lost working time. This extra expense is difficult to evaluate but could lie between SF200000 and 400000 annually. In fact, this amount would probably be sufficient to maintain permanently the quality of the treatment teams when using the classical techniques. Thus, the major economic difference between the two approaches might be in the basic investment which, for a population of three million people, is estimated at SF four million for neutron therapy and at SF two million for the optimal use of the existing techniques while the corresponding maximum expected improvement in the survival rate is 1.6 and 2.4% respectively. Thus the cost–benefit ratio for the conservative approach involving optimal use of existing techniques is about three times smaller than for neutron therapy.

Discussion

The lack of accurate data has not permitted this survey to be very precise. This brief study has been limited to Switzerland, but a similar approach is probably applicable to most Western countries, especially those with comparable health policies.

Despite the fact that some optimistic assumptions were used which were intentionally in favour of the neutron therapy, the approach consisting of an improvement in use of already existing equipment and techniques seems to be the best, at least economically speaking. Besides, it has not yet been proven that neutron therapy will solve the problem of radioresistance of some tumours, and much research and money would still be needed to find the answer. On the other hand, it is already well known how to avoid technical failures, and the only investment to ensure an optimal treatment with the existing equipment would be to improve the quality of the medical teams by training them thoroughly in cancer therapy.

The opinion of the author is that, for the reasons previously expressed, an investment in the improvement of the quality of treatment with existing equipment should have a high priority over widespread adoption of neutron beams. The latter should be used only by the very few research groups who have the required technical and clinical competence.

It is likely that a similar argument could apply to other therapy options such as high energy particle beams, and certainly to such huge installations as π meson facilities.

Yours, etc.,
J. NIEDERER,

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Hôpital Cantonal,
1211 Geneva 4, Switzerland.

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Incidence du cancer à Genève 1970/71. Registre Genevois des Tumeurs, Geneva, Switzerland.

NIEDERER, J., HAWKINS, N. V., RIDER, W. D., and TILL, J. E., 1977. Failure analysis of radical radiation therapy of supraglottic laryngeal carcinoma. *International Journal of Radiation Oncology, Biology, Physics, 2,* 621–630.

THE EDITOR—SIR,

ULTRASOUND—CURRENT STATUS AND PROSPECTS

Dr. Meire's contribution on the above topic in the series "Radiology now" (1977), though rather brief, is of interest to all radiologists and other staff who are involved in diagnostic ultrasound. The discussion is, however, limited to abdominal ultrasound and this should have been made clear, either in the title or in the text.

Many radiologists are involved in providing a diagnostic service in echocardiography and the developments and prospects in this particular application of ultrasound are both exciting and relevant. Dr. Meire states that production of rapid sequential images by real time scanners is "one of their least useful features". Not so, in cardiac ultrasound! The production of rapid sequential cross-section images of the heart has added a new dimension to non-invasive investigation of the heart and great vessels. It has made the diagnosis of complex anatomical abnormalities of congenital heart disease easier and more reliable. Important advances are also being made in the elucidation of acquired heart disease by the use of sector scanners. The teaching of echocardiography has also been facilitated by the real time scanners as the two-dimensional images show the anatomical relationships more clearly.

Yours, etc.,
D. R. NAIK.

Department of Radiology,
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REFERENCE

MEIRE, H. B., 1977. Radiology now. Ultrasound—current status and prospects. *British Journal of Radiology, 50,* 379–380.

THE EDITOR—SIR,

ULTRASOUND—CURRENT STATUS AND PROSPECTS

Dr. Naik is correct in assuming that my contribution referred only to abdominal scanning since my first sentence introduced the topic of "stored grey scale images".

I would nevertheless agree that one would hope real time scanners *should* be of particular value in cardiac diagnosis. However, I am not aware of any paper which clearly documents an improved rate of diagnostic accuracy with real time as compared with T–P scanning and I note that Dr. Naik's comments concerning its value in congenital and acquired heart disease are not supported by relevant references.

Yours, etc.,
H. B. MEIRE,
Consultant in Ultrasound.

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THE EDITOR—SIR,

TIME FOR A REALIGNMENT OF PROFESSIONAL ASSOCIATIONS OF RADIOLOGISTS?

Dr. Brindle's letter in the May 1976 issue of the BRITISH JOURNAL OF RADIOLOGY states "It (the Royal College) assumes the responsibility for negotiating with the Department of Health on professional matters". This is not quite true since the charters of each of the Royal Colleges *preclude* their involvement in terms and conditions of service which, for radiologists, are a function of the B.M.A. Radiology Group Committee. This committee is, however, also striving for closer links with the Royal College.

Yours, etc.,
F. W. WRIGHT,
Chairman, Radiologists Group Committee.

Churchill Hospital, Oxford OX3 7LJ.

REFERENCE

BRINDLE, M. J., 1976. Time for a realignment of profesional associations of radiologists? *British Journal of Radiology, 49,* 478–479.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

Radiobiology Meetings

The following meetings are scheduled:

"Early and late response of tumours at the clinical and experimental level", December 10, 1977;

"Work-in-progress", February 17, 1978;

"Recent advances in hyperthermia research", May 18, 1978.

Further information from the General Secretary, B.I.R (01-935 6237).

Tumour Ultrasound '77

An international symposium on the science and clinical practice of ultrasound diagnosis and localization of tumours will be held in London, on December 5–6, 1977. Registration and further details from Dr. Ralph McCready, Department of Nuclear Medicine and Ultrasound, Royal Marsden Hospital, Downs Road, Sutton, Surrey, U.K.

The Annual Meeting of The British Medical Ultrasonics Group

Will be held at the Institute of Electrical Engineers, Savoy Place, London, S.W.1 on December 7–8, 1977. It is intended that the programme will cover both reports on current clinical applications and also new scientific ideas and developments. Fee: Members of the BIR and HPA £7. Others £10.

Registration and further details from the General Secretary, B.I.R. (01-935 6237).

Safety, Radiological Equipment and the Law

A joint meeting of The British Institute of Radiology, the Royal College of Radiologists and the Royal Society of Medicine (Section of Radiology) will be held on January 20, 1978.

Further information from the General Secretary, B.I.R. (01-935 6237).

Carcinoma of the Bladder

A joint meeting of the Royal Society of Medicine (Section of Radiology), The British Institute of Radiology and the Royal College of Radiologists, will be held on February 17, 1978 at the RSM, London, W.1.

Details from the RSM, 1 Wimpole Street, London, W.1.

Comparison of Diagnostic Techniques for the Chest and Mediastinum

An evening meeting will be held on March 16, 1978 at The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Details and registration from the General Secretary.

BIR Annual Congress Joint Meeting and Scientific Exhibition 1978

The Annual Congress will include a joint meeting with the Royal College of Radiologists, the Royal Society of Medicine (section of radiology) and the Netherlands Society of Radiology and will be held at the R.I.B.A., London, W.1. on April 13–14, 1978. Details from the General Secretary.

The "SILVANUS THOMPSON MEMORIAL LECTURE" will be delivered at this congress by Sir John Hill, Chairman UKAEA.

Second Congress of The European Society of Nuclear Medicine

The Institute and other UK members of the European Society of Nuclear Medicine will be hosts to this congress to be held in London April 17–18, 1978. The meeting will include a commercial exhibition, scientific demonstrations and technologists sessions. Contributions of original scientific presentations and scientific demonstrations are invited. Special abstract forms, which should be returned by December 1, 1977, may be obtained from Dr. M. N. Maisey, Nuclear Medicine Department, Guy's Hospital, London, S.E.1.

BIR Conversazione

Will be held at Northwick Park Hospital, Middlesex on May 17, 1978.

Details from the General Secretary.

High Dose Rate Afterloading Gynaecological Irradiation as an Adjuvant to Gynaecological Surgery: an Assessment of the Cathetron

An evening meeting will be held on May 18, 1978 at The British Institute of Radiology (Reid-Knox Hall), 32 Welbeck Street, London W1M 7PG.

Further details from the General Secretary.

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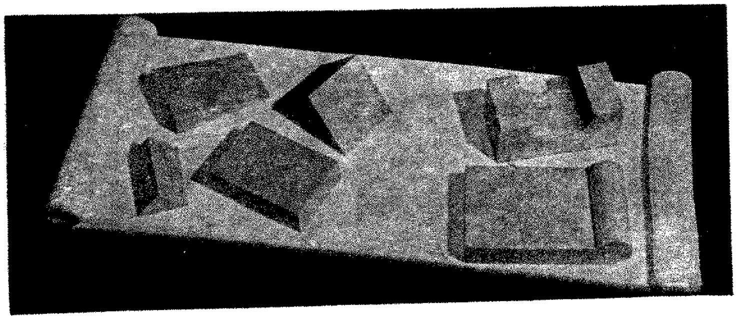

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